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METABOLIC SIGNIFICANCE OF NERVOUS SYMPTOMS DUE TO ATTACKS OF VOMITING WITH KETOSIS IN CHILDREN

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THE occurrence of nervous symptoms of variable severity is not uncommon in children presenting attacks of cyclic vomiting with ketonuria.

Some of these are related to metabolic disorders and were successively ascribed to three major factors: hypoglycemia, acidosis with ketosis, and water and electrolyte disorders.

The nervous symptoms observed at the onset of the attacks are likely to be due to hypoglycemia.

The secondary nervous symptoms occurring by the third or fourth day of an attack of vomiting with ketonuria are more difficult to interpret. They were described in France under the name of "lethargic nondiabetic acidosis" by Mouriquand and Carnet; their description was perfected by various authors (Fanconi, Nobecourt, Cathala, Lelong and Rossier, J. Marie, Bernheim) who used various terms such as ketonemia-inducing encephalitis, encephalomeningeal forms of ketonemia, fatal forms of ketonemia.

These secondary nervous symptoms were generally attributed to acidosis with ketosis. In 1953, we demonstrated that some of them were due to hypokaliemic alkalosis. They presented all the clinical and biological manifestations, and were rapidly and totally cured by the administration of potassium chloride.[1-3] Our findings were confirmed by Lelong,[4] Chaptal and associates[5] and Bernheim and François.[6]

It is our purpose to report in this article fourteen cases of severe metabolic disorders which occurred in the course of attacks of vomiting with ketonuria. We intend to demonstrate that these metabolic disorders are variant; in one case hypoelectrolytemia with extracellular hypotonia was found; in two, acidosis with ketosis, and in eleven, hypokaliemic alkalosis was demonstrated. Thus, in the present conditions of observation in France, it seems that hypokaliemic alkalosis is the most common, but not the only cause of severe nervous disorders seen in the course of attacks of vomiting with ketosis.

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MEANS OF INVESTIGATION

Our patients were investigated as follows:

(1) The usual clinical and roentgenological determinations.

(2) Chemical study of the blood.

The ionic balance of the extracellular fluids was assessed by the determination of sodium (flame photometer), of potassium (flame photometer), calcium and magnesium (method of Sobel and Hanoek[7]), chloride (modification of the method of Schales and Schales[8]), and of the proteins (method of Peters and Van Slyke).

The acid-base balance of the extracellular fluids was determined by measuring the serum bicarbonate (method of Van Slyke and Neill[9]) and the serum pH (method of Hastings and Sendroy[10]). The CO_2 tension was reckoned on the basis of the two preceding results on Van Slyke's diagram.

Ketosis was assessed through the determination of aceto-acetic acid in the blood (method of Guest and Lestradet[11]).

In addition, we determined the blood urea and sugar levels.

(3) Chemical analysis of the urine. This entailed the study of the ketone bodies,[11, 12] of urinary sodium and potassium (flame photometer), of urinary chloride,[8] and of the urinary pH.

(4) Finally, we performed repeated ECG and EEG examinations.

REPORT OF CASES

Our observations can be divided into three groups according to the metabolic anomalies encountered: metabolic alkalosis, acidosis with ketosis, and plasma hypotonia.

I. *Metabolic Alkalosis With Hypokaliemia*

The clinical pattern of this metabolic disorder was variable. In seven patients, the clinical condition was extremely severe with numerous nervous, respiratory, and abdominal signs; at times, there was cardiac and urinary involvement. In three cases, respiratory manifestations and attacks of tetany were the main features. In one case, the electrolytic disorder presented no clinical aspects.

All these children had been given sodium bicarbonate to treat the attack of vomiting with ketosis. The ingested doses were difficult to establish with accuracy because of the possible loss of a part of the drug in vomiting; nevertheless, the dose often seemed important, and in Case 7, in which there had been occasional vomiting, the child, aged 2 years, had ingested 180 Gm. of sodium bicarbonate over a period of three days.

(a) *Pictures of Metabolic Alkalosis With Hypochloremia and Hypokaliemia.*—

CASE 1 (Fig. 1 and Table I).—Patrick N., aged 5 years, well until present illness, developed an attack of vomiting with ketosis, without any apparent cause. The personal anamnesis and family past history were noncontributory.

The attack began on Nov. 15, 1952, with abdominal pain, vomiting, and loss of appetite. Later, there was a symptom-free period during which the patient received a salt-free diet. On November 22, there was a recurrence of the vomiting with diarrhea. Two days later, a significant ketosis was found, and 20 Gm. of sodium bicarbonate was prescribed. On November 25, he was in a comatose condition and had an attack of tetany.

On admission to the hospital on the morning of November 28, he was confused and delirious, unceasingly wanting to drink and immediately vomiting all that he had ingested.

Marked dehydration was present, contrasted with a slight edema of the back of the hands and of the face.

The tetanic posture of the hands and feet contrasted with an extreme muscular hypotonia.

Tendon reflexes were weak and there was a Babinski's sign on the left.

Breathing was short and superficial with pauses. The abdomen was swollen and a retention bladder was palpated.

The throat was red and there was moderate fever (38.8° C.). The urine was abundant.

Following a consultation with neurologists and neurosurgeons, the

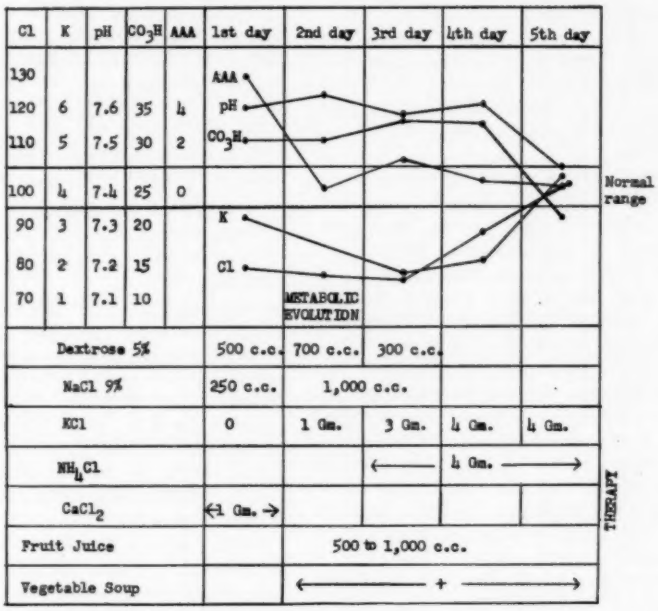


Fig. 1.—Patrick N., Case 1.

TABLE I. CHEMICAL DATA. CASE 1

	BLOOD											URINE		
DAY	pH	CO_3H (MEQ./L.)	CO_2H_2 (mM/L.)	Cl (MEQ./L.)	PROT. (MEQ./L.)	AAA (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	Ca (MEQ./L.)	GLUCOSE (GM./L.)	UREA (GM./L.)	pH	Cl (MEQ./L.)	AAA (MEQ./L.)
1st	7.60	30.5	0.97	80	17.7	5.5	140	3.3	–	–	–	–	–	+++
2nd	7.65	30.4	0.85	78	–	0	–	–	–	–	–	7.0	1.5	+++
3rd	7.57	33.6	1.07	77.5	–	1	138	1.7	4.8	1	0.33	6.5	5	15
4th	7.61	32.3	1.01	87	–	0.3	136	2.2	4.8	–	0.40	–	–	–
6th	7.46	21.8	0.87	101	16.5	0	138	4.1	–	–	–	6.5	101	0.2

child was immediately carried to the Neurosurgical Unit, with a tentative diagnosis of brain tumor or tuberculous meningitis; at the same time the metabolic investigations were continued.

The eye grounds were normal, and a trepanopuneture brought a somewhat abundant but normal subarachnoid and ventricular fluid.

The cerebrospinal fluid obtained by lumbal tapping was also normal. Cerebral ventricles were in normal position; no tumor was found.

On the other hand, laboratory determinations showed the existence of alkalosis with hypochloremia, hypokaliemia, and marked ketosis. The EKG pattern was typical of hypokaliemia.

The EEG tracing was highly abnormal with wide 2 c/s slow waves which were bilateral, symmetric, and predominant in the posterior areas.

The course was in two stages.

In the beginning, treatment consisted mainly of saline and glucose serum, and of sodium gluconate.

Ketosis was rapidly controlled, but the alkalosis and hypokaliemia increased clinically. Vomiting stopped after forty-eight hours. Consciousness returned and the tetany attacks disappeared, but the remaining clinical features were not modified, muscle weakness and hypotonia tending to increase.

Saline was then discontinued, and potassium chloride and ammonium chloride were given. Recovery was striking within twenty-four hours and only hematuria persisted for several days.

The ECG pattern varied according to the kaliemia.

The EEG tracing was normal on the sixth day.

CASE 2 (Fig. 2 and Table II).—Thimothée K., aged 14 months, was admitted on Feb. 25, 1953, with a diagnosis of encephalomeningeal syndrome.

In the past two days, he had had repeated vomiting, without diarrhea, with secondary occurrence of fever (39° C.). A physician called on the first day prescribed four daily packs of sodium bicarbonate (0.20 Gm.) and sodium sulfate (0.40 Gm.), and later, bicarbonated water which was abundantly vomited by the patient. Toward the end of the second day of the attack of vomiting, he became comatose and was taken to hospital.

The personal anamnesis and family history were noncontributory. He was born prematurely with a body weight of 2,030 grams, but his growth was normal without any incidents. Ten days before, he had had a Jennerian vaccination without appearance of vaccinal element.

On February 25, the findings, in addition to repeated vomiting, diarrhea, and fever (40° C.), were:

(1) Abdominal distention with many hydroaerial levels on x-rays.

(2) Marked dehydration with moist tongue.

(3) Superficial breathing with increased rate (40 per minute).

(4) Neurological manifestations: a semicomatose condition, a marked hypotonia, no motility of the lower limbs with very weak tendon reflexes, nystagmus-like jerks and patent Chvostek's sign, a mild stiffness of the nucha contrasting with the flaccidity of the lower limbs.

No other clinical signs were found.

Laboratory determinations showed the existence of alkalosis with hypochloremia, blood ketosis, and plasma hypertonia. The blood urea level was 1 Gm. per liter.

The CSF was normal; there was an ECG pattern of hypokaliemia.

A bacteriological examination of the stools showed a flora with predominance of gram-negative bacilli (95 per cent).

Saline and glucose serum and 3 Gm. of potassium chloride were given.

On the following day, the infant was no longer unconscious. Respiration remained rapid with pauses. Muscle flaccidity and the paralysis of the lower limbs persisted, but the

abdominal distention had disappeared. The tendon reflexes were livelier, the eye grounds normal; a blood count showed a mild hypochromic anemia with leukopenia (3,600). The humoral changes were fairly identical. The infant vomited twice.

On February 27, consciousness was normal and there was a general improvement. Tendon reflexes were lively and the infant seemed to display muscular pains; Chvostek's sign had disappeared; biological improvement was obvious.

The following day, the infant was clinically normal; this impression was confirmed by the ionogram and the EEG and ECG findings.

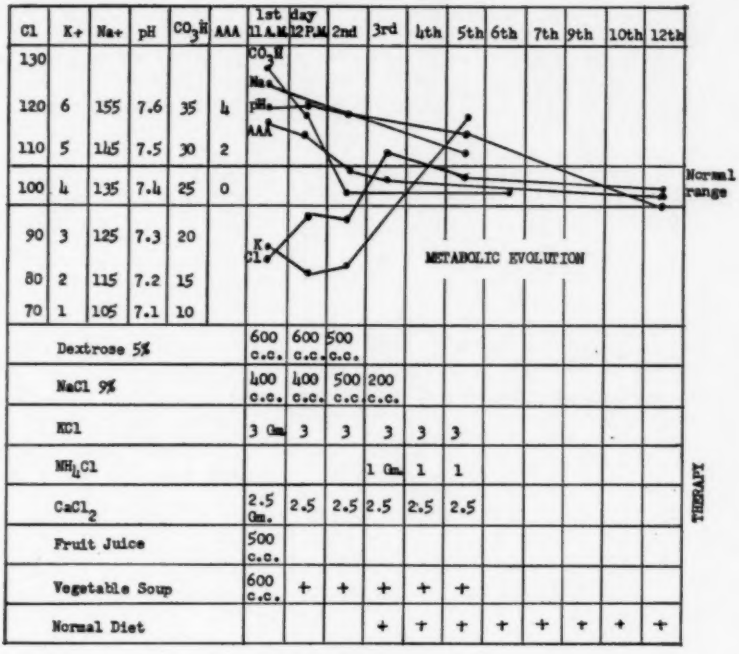


Fig. 2.—Thimothée K., Case 2.

TABLE II. CHEMICAL DATA. CASE 2

	BLOOD											URINE					
DAY	pH	CO_3H (MEQ./L.)	CO_2H_2 (mM/L.)	Cl (MEQ./L.)	PROT. (MEQ./L.)	AAA (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	Ca (MEQ./L.)	GLUCOSE (GM./L.)	UREA (GM./L.)	pH	Cl (MEQ./L.)	AAA (MEQ./L.)	K (MEQ./L.)	Na (MEQ./L.)	VOL. (C.C.)
1st	7.57	39	1.25	88	15	3	158	1.8	4.8	1.26	1	5.6	6	4	87	20	110
2nd	7.60	33	0.88	98	–	0.8	–	2	–	–	–	6	24	1	62	8	160
3rd	7.56	23	0.78	109	–	Traces	–	–	–	–	–	6.5	34	0.4	16	24	160
4th	–	–	–	–	–	–	–	–	–	–	–	6	40	0	11	35	325
5th	7.49	23	–	101	12	–	144	6	–	–	–	5.6	290	0	55	137	325
6th	–	–	–	–	–	–	–	–	–	–	–	5.8	220	0	240	127	250

CASE 3 (Fig. 3 and Table III).—Louis D., aged 6 years, was admitted to the hospital on April 14, 1953, for vomiting and diarrhea.

He had previously had similar attacks of diarrhea but they had never been so severe.

The present attack started on April 5, with abundant vomiting. On April 7, the stools were decolorated. On April 10, diarrhea occurred, 10 stools daily, and the vomiting had become intractable at any attempt to ingest food. Diffuse abdominal pains occurred.

At this time, thirst was marked. There was no fever.

On April 14, a doctor prescribed DCA and sodium bicarbonate. The condition deteriorated, leading to admission of the patient to the hospital.

Examination on admission showed a semicomatose, feverless child. The extremities were cold and cyanotic. There was no meningeal involvement; muscle hypotonia was marked with

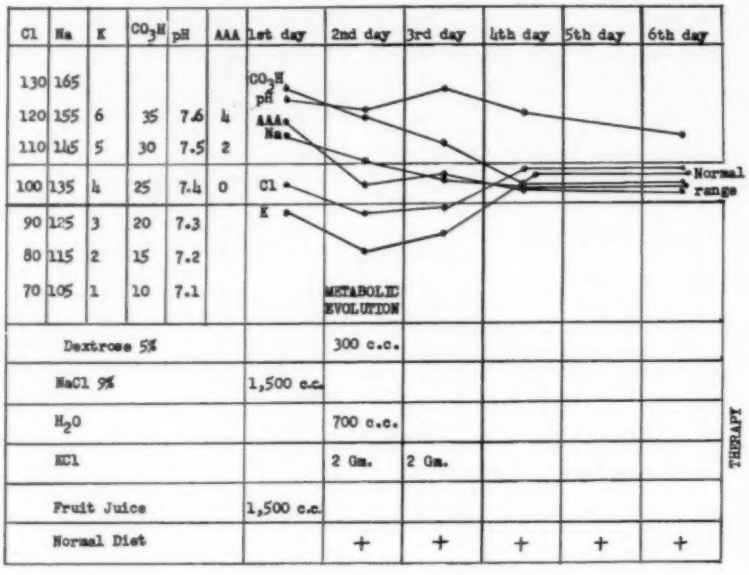


Fig. 3.—Louis D., Case 3.

TABLE III. CHEMICAL DATA. CASE 3

	BLOOD								URINE			
DAY	pH	CO_2H (MEQ./L.)	CO_2H_2 (MEQ./L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	PROT. (MEQ./L.)	VOL. (C.C.)	Na (MEQ./L.)	K (MEQ./L.)	Cl (MEQ./L.)
1st	7.61	38.0	1.18	3	100	152	3.4	-	750	72	10.5	42
2nd	7.57	34.5	1.15	0	94	140	2.4	17.5	1,000	98	11.5	67
3rd	7.62	30.0	0.88	Traces	95	133	2.8	15.2	750	98	8.0	67
4th	7.58	25.0	0.80	0	104	133	4.3	-	600	-	-	-
5th	-	-	-	-	-	-	-	-	500	-	-	-
6th	7.53	25.0	0.90	0	104	138	4.2	-	250	-	-	-

normal tendon reflexes. Respiration was slow and abdominal in type. Blood pressure was 80/65. Dehydration was marked, contrasting with an edema of the back of the hands.

Thirst was intense and the child unceasingly asked to drink, ingesting 3 liters of fluid in the afternoon. No other pathological signs were found. Blood determinations confirmed the tentative diagnosis by showing the presence of alkalosis, blood ketosis, and plasma hypertonia. On the first day, the hypokaliema was mild (3.4 meq.).

The clinical course improved within twelve hours, during which the child ingested 3 liters of fluid (isotonic saline and fresh fruit juice). On the following day, plasma hypertonia and ketosis were controlled. Alkalosis had decreased, but hypokaliemia became more apparent with a related EKG pattern.

Two grams of potassium chloride was given daily. The EEG tracing showed numerous, more or less wide, slow waves of 3 to 5 c/s with posterior predominance.

The biological disorders disappeared by the fourth day and the child displayed no clinical or electrical anomaly.

CASE 4 (Fig. 4 and Table IV).—Jean-Pierre H., aged 3 years, was sent to our Unit on Dec. 2, 1953, for vomiting.

On November 30, this child, till then in good health, suddenly developed severe vomiting, without fever but with ketonuria. The treatment prescribed included sugar and Vichy water, containing 6 Gm. of sodium bicarbonate per liter. During the night, he was very disturbed and had an intense thirst. On the following day diarrhea began. Two more

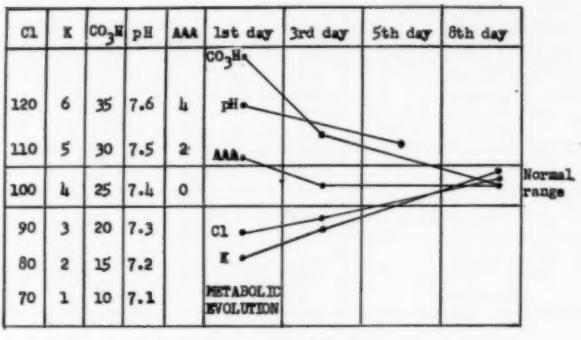


Fig. 4.—Jean-Pierre H., Case 4.

TABLE IV. CHEMICAL DATA. CASE 4

	BLOOD								URINE			
DAY	pH	CO_3H (MEQ./L.)	CO_2H_2 (MEQ./L.)	AAA (MEQ./L.)	K (MEQ./L.)	Na (MEQ./L.)	Cl (MEQ./L.)	PROT. (GM./L.)	VOL. (C.C.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)
1st	7.60	41.1	1.3	0.5	2.2	140	89	63	-	-	-	-
2nd	-	32.6	-	-	2.9	140	92	-	250	2.4	124	28
8th	7.57 (5th day)	26.2		-	4.3	140	102	63	-	-	-	-

liters of Vichy water were given. On this day, the doctor noted fever (39° C.), drowsiness, and a pain in the appendicular area.

On admission to hospital, the child was prostrated and lethargic.

The abdomen was distended and over-all tender. On x-rays, the diaphragm was abnormally high. There were many hydroaerial levels (Fig. 8). Rectal examination was noncontributory.

The child had been given 300 ml. of 5 per cent dextrose solution, 300 ml. of orange juice, and 300 ml. of isotonic saline prior to the blood examinations, which showed alkalosis with hypokaliemia and mild ketosis.

On the following day, December 3, the child was clinically normal, but the metabolic syndrome was practically identical. Kaliemia was 2.9 meq., with an ECG pattern of hypokaliemia.

On December 4, the ionogram returned to normal, the EEG tracing was normal, and recovery complete.

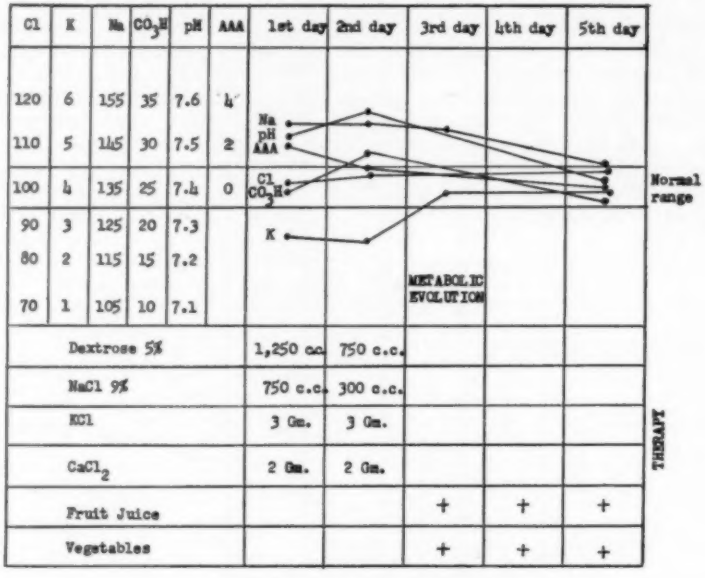


Fig. 5.—Sylvie H., Case 5.

TABLE V. CHEMICAL DATA. CASE 5

	BLOOD									URINE				
DAY	pH	CO_2H (MEQ./L.)	CO_2H_2 (MM./L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	Ca (MG./L.)	PROT. (MEQ./L.)	VOL. (C.C.)	Na (MEQ./L.)	K (MEQ./L.)	Cl (MEQ./L.)	pH
1st	7.52	25.0	-	2	101	150	2.8	-	17.7	-	-	-	-	-
2nd	7.57	28.1	0.95	Trace	107	150	2.7	86	13.4	-	-	-	-	-
3rd	-	-	-	-	-	149	3.8	-	-	400	205	16	175	-
4th	-	-	-	-	-	-	-	-	-	325	157	12	93	8
5th	7.42	22.3	1.0	0	108	140	4.1	-	16.3	-	-	-	-	-

CASE 5 (Fig. 5 and Table V).—Sylvie H., aged 2 years, had been tired for five days, when she developed on March 13, 1954, diarrhea and persistent vomiting, first of food and later of bile. On the following day, her condition deteriorated and she was given sodium bicarbonate which she vomited.

During the night, she became unconscious and hypotonic. She was given 250 ml. of glucose serum and 250 ml. of saline. Her condition failed to improve and she was admitted to the hospital.

In her family history, several facts were of significance: the mother had urticaria and eczema, the father had had attacks of diarrhea with vomiting; a 4-year-old sister had had, since the age of 2, attacks of vomiting with ketonuria, always followed by prurigo strophulus.

At the age of 17 months there had been an attack of ketonuria followed by prurigo strophulus.

On March 15, she was drowsy and lethargic, with extreme muscular hypotonia. The movements of the limbs were very reduced, but paraplegia was not in question.

Dehydration was marked with a dry, rasped tongue, and the skin was inelastic.

Tendon reflexes were weak and variable.

Respiration was superficial.

The abdomen was distended and tympanic.

No abnormal cardiac or pulmonary manifestations were noted.

In the evening, the temperature rose to 39.2° C., with a pulse rate of 130 to 140.

Blood examination showed the existence of alkalosis with hypokaliemia, ketonemia, with mild plasma hypertonia.

The ECG tracing was typical of hypokaliemia.

The EEG tracing was abnormal: very wide slow waves of 2 to 3 c/s, generalized and symmetric with posterior predominance.

On the following day, there was a marked improvement as a result of the administration of potassium chloride and rehydration; only the abdominal distention increased, requiring rectal catheterization.

The biological syndrome was poorly modified, as was the ECG.

On the third day, the child was well, diarrhea had stopped. The EEG showed only some isolated slow waves of 3 to 4 c/s, of small amplitude, posterior and symmetric.

On March 22, the child was well.

CASE 6 (Fig. 6 and Table VI).—Catherine L. is a 22-month-old infant, single child of healthy parents. On the day following Christmas, she developed an attack of repeated vomiting with ketosis, which was treated with sugar, sodium bicarbonate, and chlorpromazine. Vomiting persisted for three days. Some diarrheic stools were passed, and then deep drowsiness developed. On admission to the hospital the examination showed a dehydrated infant in a condition of deep lethargy; vomiting had stopped. It was difficult to arouse her. Respiration was quiet, slow, and superficial. Hypotonia was very marked without areflexia or paralysis. The abdomen was soft and painless; there was no meningeal involvement, no Chvostek's sign. The tongue was moist and the heart normal. A mild rhinopharyngitis was present.

The laboratory findings showed alkalosis, hypochloremia, and hypokaliemia. Three grams of potassium chloride, 500 ml. of Ringer's solution, fruit juices, and sugar water orally were prescribed. The EEG tracing showed diffuse and synchronous slow waves.

In the morning of the following day, the findings were similar, but the patient was more alert although still drowsy. The complexion was colored, the tongue moist, and respiration still superficial. Blood fasting sugar: 1 Gm. per cent. The CSF was normal.

The infant was given, over a period of twenty-four hours, 1,000 ml. of Ringer's solution and 3 Gm. of potassium chloride.

On the following day, the infant's condition had improved, she was more alert and breathing was nearly normal. She was still thirsty and remained hypotonic. The metabolic seventh day. Food intake was normal after several days.

CASE 7 (Fig. 7 and Table VII).—Frederic D., a 26-month-old male child, had a history of repeated vomiting for three days, associated with intense diarrhea and dehydration. Ketone was found in the urine and

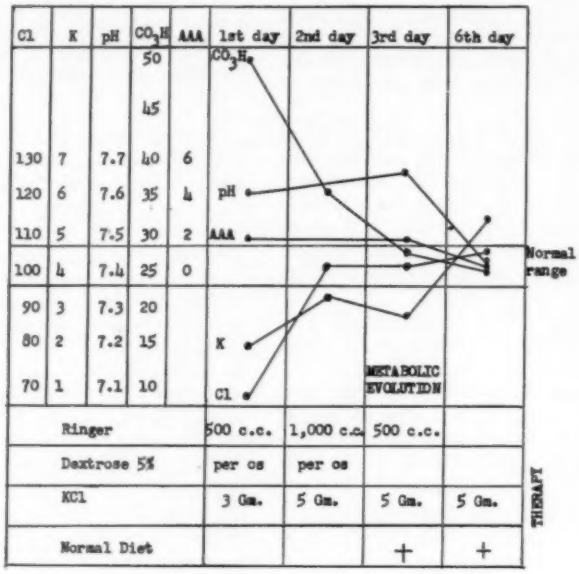


Fig. 6.—Catherine L., Case 6.

TABLE VI. CHEMICAL DATA. CASE 6

	BLOOD								
DAY	pH	CO_3H (MEQ./L.)	CO_2H_2 (MM./L.)	Cl (MEQ./L.)	PROT. (MEQ./L.)	AAA (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	GLUCOSE (GM./L.)
1st	7.59	53	2.3	72	15	++	146	2	1.08
2nd	—	34	—	100	—	—	150	3.3	—
3rd	7.62	27	0.8	100	11.5	+	142	2.9	—
6th	7.41	24	1.12	103	15	0	135	5.6	—

disorders began to disappear, but as plasma potassium remained low, 5 Gm. of potassium chloride was prescribed daily.

On the following days, the condition returned to normal. The digestive, respiratory and nervous disorders disappeared and the potassium chloride was discontinued by the sodium bicarbonate prescribed; the child's condition deteriorated. He ingested during three days a large amount of sodium bicarbonate, in all some 180 Gm.

The child's past history was noncontributory, but his sister had developed a similar affection which was

better tolerated and of shorter duration.

By the third day of the disease, he was sent by plane from Libreville (Africa), where he lived, to Paris, on account of his severe condition. During the flight he became unconscious and had six convulsive fits of short duration.

and no Chvostek's sign; hypotonia was very marked, the tendon reflexes were absent, no Babinski's reflex could be elicited.

Blood chemical determinations showed a mild ketosis and hypochloremic alkalosis with hypokaliemia.

Five hundred milliliters of a 9 per cent sodium chloride solution and 4

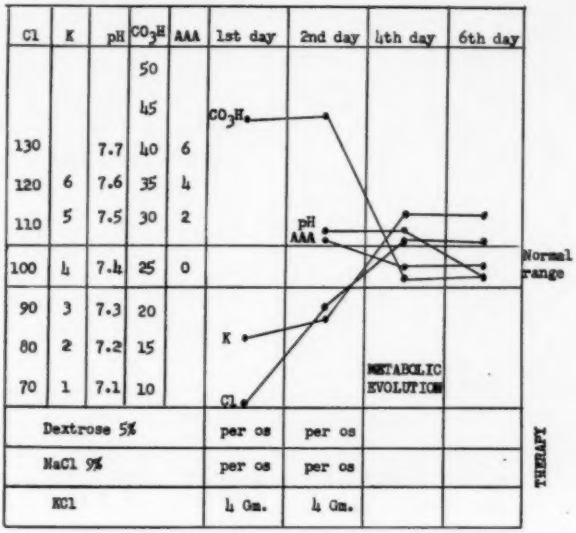


Fig. 7.—Frederic D., Case 7.

TABLE VII. CHEMICAL DATA. CASE 7

	BLOOD									
DAY	pH	CO_3H (MEQ./L.)	CO_3H_2 (mM/L.)	Cl (MEQ./L.)	PROT. (MEQ./L.)	AAA (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	UREA (GM./L.)	GLUCOSE (GM./L.)
1st	—	43	—	67	16.5	—	143	2.3	1	1
2nd	7.46	43	1.95	89	11	+	150	2.6	—	—
4th	7.44	22	0.98	107	12	0	132	5.9	—	—
6th	7.39	22	1.12	107	14	0	137	5.7	—	—

On admission to the hospital, the child was severely dehydrated, comatose, and at times his eyes were revulsed. He was pale and mildly cyanotic. The heart was normal, the pulse rate 140, the blood pressure 110/60, the temperature 40° C.

There was an abdominal distention, respiration was superficial with arrests; there were no meningeal involvement

Gm. of potassium chloride per os were prescribed.

On the following day, the child was conscious and had no further convulsive attacks. He was thirsty and drank much without vomiting. Muscle hypotonia and superficial breathing persisted.

The ECG tracing displayed flat T waves. The EEG pattern was highly

abnormal with diffuse slow waves. The chemical blood findings were slightly improved.

Four grams of potassium chloride daily were prescribed.

On the following days, the clinical manifestations progressively improved; by the third day of treatment the breathing returned to normal; muscle hypotonia lasted till the fifth day, and by the sixth day, the metabolic disorders disappeared.

After seven days potassium chloride administration was discontinued, the child being normal again.

To summarize, in seven cases of vomiting with ketosis, we found a severe condition related to metabolic alkalosis and hypokaliemia. The children's ages ranged from 1 to 6 years. Some had displayed repeated attacks and some were affected for the first time. Vomiting was always severe and the children had been given sodium bicarbonate in unprecise amounts. The clinical manifestations, resulting from the humoral unbalance, appeared from the third to the fifth day following the onset of vomiting.

The clinical picture was similar to that described in other etiological varieties of metabolic alkalosis with hypokaliemia. It assumed such a severity that it differed from other cases.

Nervous and muscular involvement always predominated. The disturbances in consciousness ranged from indifference to lethargy and coma. Decrease in muscle strength and tonus was a constant finding. Periosteal reflexes were either abolished, weak, or normal; twice Babinski's sign was noted. Four patients developed a flaccid quadriplegia. The cranial nerves were not affected in our patients. At times with this background of hypotonia and paralysis, there were transient attacks of tetany and a Chvostek's sign.

The other signs were also important. In five cases, there was fast and superficial breathing with periods of apnea. Five patients developed a paralytic ileus causing abdominal distention with numerous hydroaerial levels at the x-ray examination (Fig. 8). There were no symptoms of cardiovascular involvement but in every case the ECG pattern was abnormal. Dehydration was mild or marked, and thirst was often very marked. The tongue was always moist. In three patients a moderate edema of the feet and hands was noted. In most cases, renal involvement was not apparent. In one patient hematuria and a paresia of the bladder occurred with urine retention.

These various features were manifested in several evolutive pictures, with simultaneous or successive association of the renal, respiratory, and nervous manifestations of metabolic alkalosis and the neuromuscular, cardiac, and abdominal signs of hypokaliemia.

The chemical study of the blood in every case showed the typical features of the syndrome of alkalosis with hypochloremia and hypokaliemia. These findings are reported on the tables corresponding to each history: pH and the bicarbonate level are high; chloremia and kaliemia are lowered. Sodium is normal or slightly elevated. In addition, and this is an original feature of our cases as compared with other histories of alkalosis with hypokaliemia, the blood level of ketonic bodies is increased. We assayed it through a determination of the aceto-acetic acid (AAA) which

rose sometimes to levels as high as 5 meq. per liter. It should be noted that the presence of ketonic acids in practically fasting children, a decreased output of chloride and sodium, and a fairly normal urinary

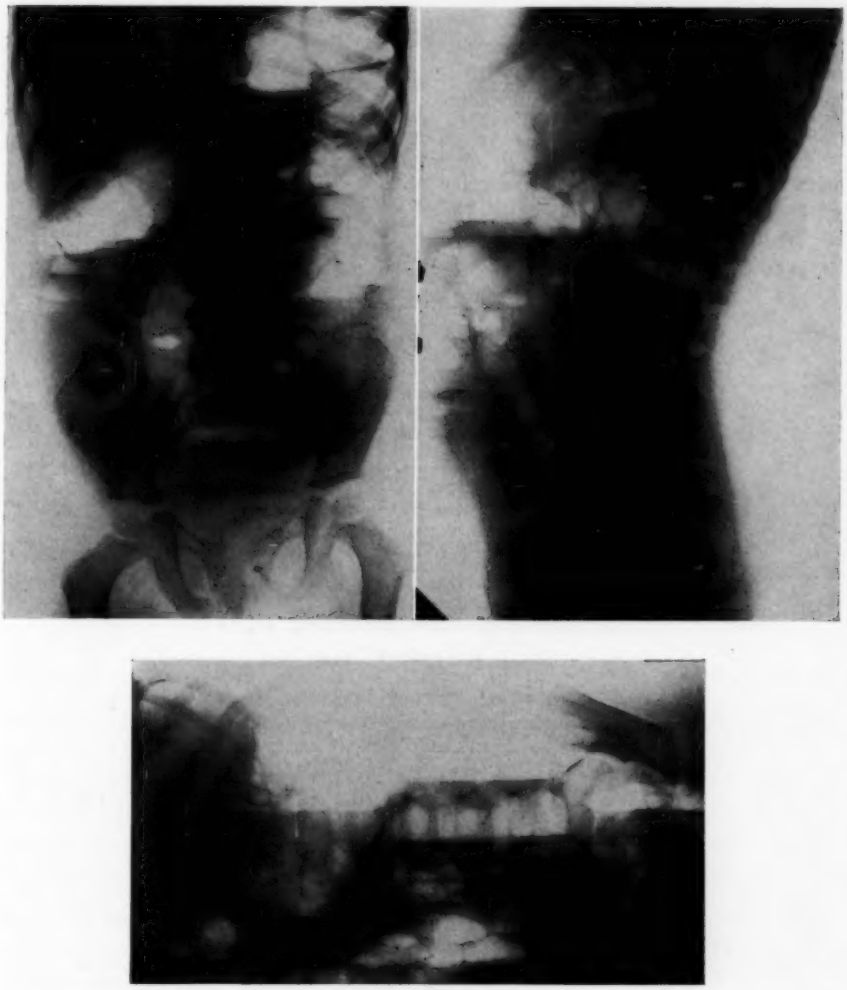


Fig. 8.—Hypokaliemic paralytic ileus.

large amounts is far from controlling alkalosis on account of the marked degree of hypochloremia.

Urinalysis showed a marked ketonuria, a large output of potassium in pH, less alkaline than could be inferred from the blood findings.

ECG tracings were valuable. The ECG record in every case showed the usual pattern of hypokaliemia:

lengthened Q-T interval, flat or absent T wave, possible depression of the S-T internal, and inconstant presence of U waves. In all cases, the EEG pattern was highly abnormal. The tracings showed diffuse and synchronous slow waves that rapidly disappeared with treatment of the metabolic disorder.

The course was favorable. All the patients recovered despite the severity of their condition on admission. Sodium chloride alone, or associated with ammonium and calcium chloride, was ineffective or of little value. On the contrary, potassium chloride proved to be highly effective: the clinical manifestations improving within twenty-four hours and disappearing within two or three days; the blood chemical abnormalities disappeared somewhat more slowly, taking three to five days. The ECG and EEG patterns became normal within five to twelve days.

(b) *Picture of Tetany Due to Alkalosis.*—

CASE 8 (Fig. 9 and Table VIII).—Jacqueline L. was staying in a holiday camp when she developed vomiting with ketonuria. The doctor prescribed sodium bicarbonate of unspecified dosage. Tetany developed on Aug. 13, 1954.

In her anamnesis, a glycosuria had been noted two years before.

In our Unit, we noted an erythematopultaceous angina with a temperature of 38.3° C. The examination showed only Chvostek's sign. Blood calcium was normal, but she had been given calcium.

On the first day, the laboratory studies showed alkalosis with hypokaliemia, although the clinical condition was satisfactory. The ECG was normal despite a decreased plasma level of potassium. On the first day, the EEG tracing showed a disturbed pattern with bursts of generalized slow waves. Potassium chloride was prescribed.

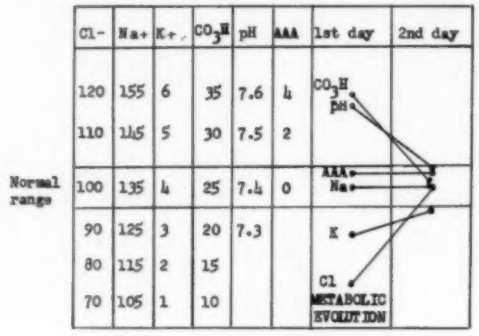


Fig. 9.—Jacqueline L., Case 8.

TABLE VIII. CHEMICAL DATA. CASE 8

	BLOOD									
DAY	pH	CO_3H (MEQ./L.)	CO_3H_2 (mM/L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	PROT. (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	Ca (MEQ./L.)	DEXT. (GM./L.)
1st	7.60	35.5	1.1	Traces	78	18.7	135	2.7	4.5	
2nd	7.47	27.7	1.1	Traces	96	16	133	3.4		
4th	-	-	-	-	-	-	-	-	-	0.72

On the following day (August 14) the metabolic abnormalities had disappeared and the EEG was normal.

CASE 9 (Fig. 10 and Table IX).—Danielle O., aged 7 years, was sent to the hospital on the evening of March 24, 1954, for vomiting and ketonuria. The attack had begun on March 21, by cephalalgia and right otalgia. At noon on the following day she started vomiting food, which was followed by bile-stained vomitus. Temperature was normal. During the two following days, the condition deteriorated and dehydration increased despite unsuccessful attempts of her doctor to rehydrate her with a dextrose solution.

Frequent attacks of vomiting with ketonuria had occurred since the age of 2 years.

In the night of March 24-25, she was weary, but conscious. She was thirsty and markedly dehydrated with a dry tongue. During the night she drank two liters of a bicarbonate solution containing 16 Gm. per liter.

On the following day, she was agitated, confused, and hostile, and the examination showed a marked dehydration. Tendon reflexes were active, Babinski's sign was not found. There was a Chvostek's sign.

Some stiffness and a triggerlike attitude led to a lumbar tapping which showed a normal CSF. The eye grounds were normal. There was no fever. Diarrhea then set in.

The chemical determinations showed the existence of alkalosis with hypokaliemia and blood ketosis. The EEG record showed sinusoidal 2.5 to 3 c/s slow waves in symmetric hypersynchronous bursts.

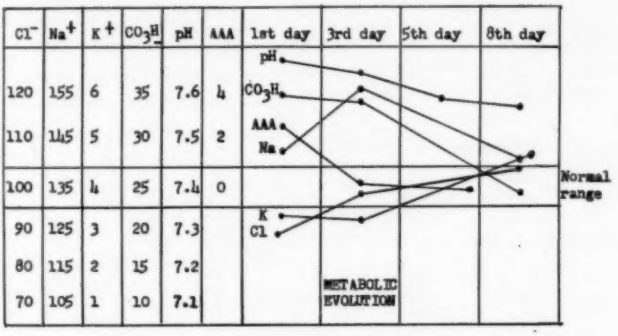


Fig. 10.—Danielle O., Case 9.

TABLE IX. CHEMICAL DATA. CASE 9

	BLOOD							
DAY	pH	CO_3H (MEQ./L.)	CO_2H_2 (mM/L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	PROT. (MEQ./L.)
1st	7.73	37.4	0.85	3	88	144	3.3	-
3rd	7.68	34.3	0.86	0	100	150	3.3	16
8th	7.58	24.6	0.78	0	105	142	4.6	14.7

Following rehydration with sugar water and fruit juices, the change was dramatic, and on the next day only the diarrhea persisted. The EEG showed a little improvement.

On March 27, the abnormal clinical findings had disappeared, but the ionogram remained abnormal and only ketosis had disappeared. The ECG was only slightly modified despite a blood potassium level of 3.3 meq. per liter and a sodium level of 160 meq. On that day, the EEG showed some posterior slow waves.

The tracing was nearly normal on March 29 and the next ionogram (on April 1) was normal.

CASE 10 (Table X).—Nicole D., a 9-year-old girl, had a history of frequent attacks of "vomiting with ketonuria" since the age of 3 years. There had been for two days before admission intractable vomiting with diarrhea. She was given sodium bicarbonate, 15 Gm., on the eve of hospitalization.

On admission on Sunday evening, she displayed: (1) such a marked thirst that the mother accompanying her had a bottle of water in the hand; (2) a normal sensorium; (3) a tetany with typical contracture of the limbs and muscle jerks; (4) a shallow respiration.

Neither the reflexes nor deglutition was modified. The pulse was regular.

TABLE X. CHEMICAL DATA. CASE 10

	BLOOD							
DAY	pH	CO_2H (MEQ./L.)	Cl- (MEQ./L.)	AAA (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	Ca (MEQ./L.)	UREA (GM./L.)
1st		29	88	-	144	3.2	5	0.53
4th	7.50	24	93	0	-	4.2	5	0.15

The blood pressure was 95/40 mm. Two hours after admission the contractures had decreased but athetoid movements of the fingers and toes had set in. The eye grounds were normal.

Blood examination on admission showed hypochloremic alkalosis with hypokaliemia, plasma hypertonia, and normal calcium.

She was given isotonic saline, 6 Gm. of calcium chloride, and 6 Gm. of potassium citrate.

By Monday, clinical recovery had occurred, but the ECG tracing pointed to hypokaliemia. The electromyogram showed no sign of tetany.

On Wednesday, the clinical, ECG, and chemical examinations were normal.

In summary, in three children with cyclic vomiting and ketosis, aged 3 to 9 years, given sodium bicarbonate, we noted a clinical picture fairly different from the previously described one.

The only abnormal manifestations displayed by these children were: (1) fits of tetany with Chvostek's sign, contractures of the limbs and sometimes convulsions; (2) superficial breathing; (3) marked thirst. These histories were related to the former cases by the blood findings. There was in all three a metabolic alkalosis with hypokaliemia. Hypokaliemia was less marked than in the former cases, the lowest level being 2.7 meq. per liter and usually it was 3 to 3.4 meq. per liter. It is likely that the mild character of hypokaliemia accounted for the lack of neuromuscular manifestations of potassium deficiency, and for the occurrence of tetany induced by alkalosis which is prevented by high hypokaliemia. In all these cases blood calcium was normal.

In only one were the ECG anomalies related to hypokaliemia. On the contrary, the EEG tracings were completely similar to those of the former group, with diffuse synchronous slow waves.

(c) *Alkalosis With Symptom-Free Hypokaliemia.*—

CASE 11 (Fig. 11 and Table XI).—Dominique M., aged 4 years, was admitted to hospital for intractable vomiting with ketosis on Dec. 28, 1954.

He was an allergic child who suffered from facial eczema in his first year of life. He had an attack of vomiting with ketosis a month previously. He had six siblings, one of whom is also affected with cyclic vomiting, and another died at the age of 2½ years in the course of an attack of vomiting with ketosis. On admission to hospital, Dominique had been vomiting copiously for two days; he drank little and displayed no abnormal clinical and especially neurological or abdominal manifestation. He was somewhat dehydrated and the tongue was very dry. On the previous day he had been given 40 ml. of 9 per cent saline, 1.5 Gm. of potassium chloride, and 300 ml. of a bicarbonate mineral water.

The blood findings were: alkalosis with a very mild hypokaliemia without clinical manifestations. Ketosis was moderate.

The following treatment was prescribed: 1 liter of 5 per cent dextrose solution, 1 liter of 9 per cent saline and 2 Gm. of potassium chloride. Vomiting stopped and recovery took place within twenty-four hours.

This clinical history is interesting because of this mild symptom-free humoral disorder. It is likely that the early administration of potassium, despite the ingestion of a bicarbonate solution, played a preventive part on the development of the syndrome.

In summary, this is a case of cyclic vomiting with ketosis without serious clinical signs, but with the laboratory findings showing a moderate rise of the bicarbonate and a mild decrease in the potassium and chloride levels. These chemical anomalies subsided within two days.

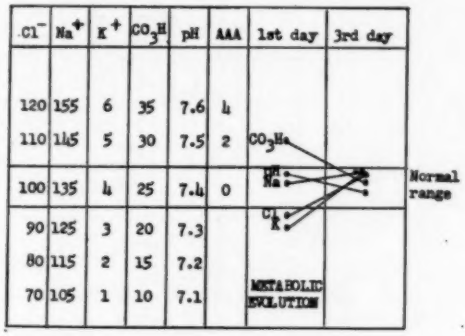


Fig. 11.—Dominique M., Case 11.

TABLE XI. CHEMICAL DATA. CASE 11

	BLOOD							
DAY	pH	CO_3H (MEQ./L.)	CO_3H_2 (mM/L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	PROT. (MEQ./L.)
1st	7.42	31	1.35	+	94	140	3.2	16.6
3rd	7.37	27	1.35	∓	103	147	4.5	17.1

II. *Acidosis With Ketosis*

In two children affected with cyclic vomiting, the clinical accidents observed were related to acidosis with ketosis.

CASE 12 (Fig. 12 and Table XII).—Gerard L., aged 6 years, was sent to our service on Jan. 19, 1954, for vomiting with ketosis.

On January 16, he had developed a nasal discharge and, despite treatment, breathing was more difficult on the following day. On January 18 intractable vomiting developed, which led to rapid dehydration and deterioration of the general condition, requiring admission to hospital.

He was born in the Guadeloupe (French Antillas) and had attacks of asthma until 2 years of age. The attacks occurred about once a month and the course was always the same: at the onset, nasal discharge and sneezing, followed by the attack of asthma itself and in the end the development of severe vomiting. The usual duration was twenty-four to forty-eight hours, but previously symptoms of such a severity had never been observed. There was a history of two brothers and two uncles with asthma.

On January 19, physical examination showed a dehydrated, depressed, lethargic child. The tongue was dry and he desired to drink unceasingly.

Respiration was *ample,* slow, deep, of the Kussmaul type. The breath has a marked smell of ketone. The heart was regular with a rate of 180 per minute. The blood pressure was 100/70.

There was no abdominal spasm but a retention bladder was felt. The rest of the examination was noncontributory.

The ionogram showed the presence of mild acidosis with strong ketosis.

The child was rehydrated by intravenous infusion of 250 ml. of 5 per

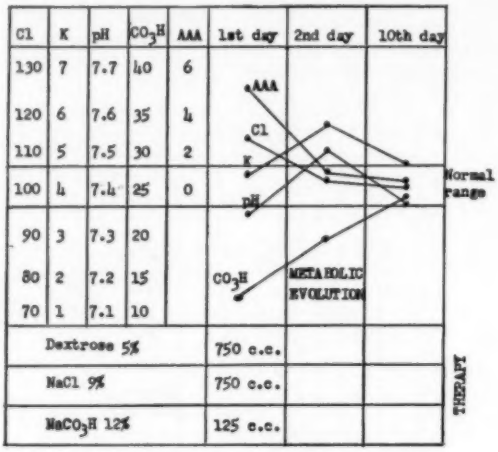


Fig. 12.—Gerald L., Case 12.

TABLE XII. CHEMICAL DATA. CASE 12

	BLOOD								URINE					
DAY	pH	CO_2H (MEQ./L.)	CO_2H_2 (mM/L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	PROT. (GM./L.)	TOTAL (C.C.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	AAA (MEQ./L.)	pH
1st	7.32	12	0.65	3	105	136	4.3	84	250	4	107	40	30	—
2nd	7.48	20	0.82	0.5	101	138	5.5	65	950	32	37	20	++	—
10th	7.37	23	1.22	0	100	136	4.8	65	350	150	100	90	0	5.5

cent glucose serum and 250 ml. of 9 per cent saline, and orally with 500 ml. of glucose serum, 500 ml. of saline and 125 ml. of 12 per cent bicarbonate serum.

On the following day, improvement was striking with only the persistence of a somewhat ample respiration. Recovery was rapid.

In this child, in the course of an attack of asthma, vomiting resulted in a marked ketosis with acidosis.

following any attempt to give food or fluids.

She was very tired and drowsy, and complained of vague abdominal pains. Temperature was normal.

At examination, no definite pathological findings were found except dehydration. All fluids ingested were vomited; respiration was ample and slow.

The ionogram showed marked ketosis with acidosis. Rehydration by hypo-

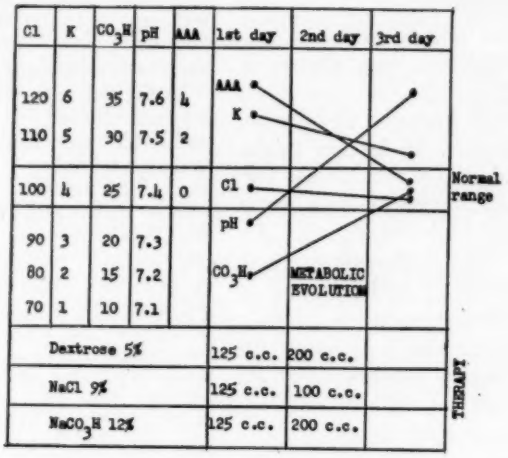


Fig. 13.—Marie-Chantal M., Case 13.

TABLE XIII. CHEMICAL DATA. CASE 13

	BLOOD							
DAY	pH	CO_2H (MEQ./L.)	CO_2H_2 (mM/L.)	AAA (MEQ./L.)	Cl (MEQ./L.)	Na (MEQ./L.)	K (MEQ./L.)	PROT. (GM./L.)
1st	7.35	14.5	0.75	5	100	138	5.2	78
3rd	7.65	25.1	0.70	0	98	140	4.5	60

CASE 13 (Fig. 13 and Table XIII).—Marie-Chantal M., aged 4 years, was admitted to the Unit for vomiting.

She had a history of measles at the age of 1 year, and varicella at the age of 3 years. Parents were healthy. For the past one and one-half months sleep was bad and appetite poor. The child was enuretic. For a week she had complained of cephalalgia, especially on waking in the morning, with nausea and photophobia. Three days before admission, vomiting developed

dermoclysis was carried out and 1/8 mg. of atropine sulfate was prescribed. On the following day, vomiting decreased. Subcutaneous and rectal rehydration was continued and 25 mg. of Phenergan and 0.06 Gm. of phenobarbital were prescribed in addition.

On January 4 the child was well and the vomiting and cephalalgia had disappeared. The ionogram returned to normal but pH was very high. This fact seems to be explained by the restlessness and the breathlessness of the

child during the venepuncture. The blood count showed 34,000 leukocytes with 21 per cent polymorphonuclear cells.

In this child there was acidosis with ketosis, with mild clinical findings and rapid recovery.

In summary, these two children, aged, respectively, 4 and 6 years, presented an attack of cyclic vomiting with ketosis. Neither had ingested sodium bicarbonate.

The most constant clinical sign was hyperpnea which was very intense in the two children. One was comatose, the other a little drowsy. The former had a dry tongue, an intense thirst, and presented urine retention. The blood chemical study in both cases showed a very high ketosis with decreased pH and bicarbonate level, a normal chloride level, and a normal or slightly increased potassium level.

The administration of sugar, a sodium bicarbonate solution, and an isotonic solution of sodium chloride brought about a rapid recovery.

The amounts of sodium bicarbonate required were moderate: 125 and 325 ml., respectively, of a 12 per cent solution (or 1.5 to 4 Gm. of sodium bicarbonate) because of the rapid disappearance of ketosis under the action of carbohydrates.

III. *Coma With Plasma Hypotonia*

CASE 14.—Martine R., aged 9 years, was hospitalized on June 27, 1954, for intractable vomiting, a subcomatose condition and restlessness.

The first pathological manifestations occurred on June 12. Since that date, she had been tired, had a poor appetite, and complained of cephalalgia. Her condition changed on June 22. She was very pale, the temperature was 39° C. She complained of marked cephalalgia. The temperature remained high and on the evening of June 24 she developed nausea with vomiting. On June 25, following a seeming improvement in the child's condition during the day, profuse vomiting set in in the evening. On the following day the vomiting continued and the breath had a strong smell of ketone.

The physician then prescribed sodium bicarbonate in enemas and orally, but apparently it was lost by these two routes. In the evening she was agitated and complained of abdominal pains. During the night she became unconscious and delirious.

In the morning of June 27 the examination showed a pale, dehydrated child; she was agitated, unconscious, and was vomiting. The plantar reflex elicited an extension of the big toe.

The temperature was 36.6° C. and the blood pressure 90/60 mm. The eye grounds and CSF were normal. A metabolic disorder was considered as possible, as there was a strong ketonuria and a mild ketonemia. The laboratory findings were as follows: urea, 0.97 Gm. per cent; pH, 7.51; CO_3H, 29.8 meq.; CO_3H_2, 1.08 mM per liter; AAA, traces; Cl, 88 meq.; Na, 130 meq.; K, 4 meq.; proteins, 17.76 meq.

The ECG tracing was normal.

Blood count: 4,630,000 red blood cells, 6,200 white blood cells with 69 per cent polymorphonuclear cells.

Supportive treatment was carried out: phenobarbital, Largactil, Phenergan, and rehydration by hypodermoclysis with 500 ml. of glucose serum and 250 ml. of saline.

In the night, the child's condition gave concern, but on the following day she was better, although still confused. On June 29 she was practically normal. The examination was noncontributory. The blood urea level was 0.72, the fasting blood sugar 1.04. The EEG tracing was slightly altered without localization changes. From that time on, as the child recovered, the urea level progressively fell to 0.40 on July 2 and 0.15 on July 10. Over this

period she vomited three times. During the whole duration of disease, diuresis was good, ranging from 500 to 1,000 ml. daily.

The metabolic origin of the affection is certain. The neurological features were of short duration, and recovery took place without sequelae and further the CSF and eye grounds were normal.

The increased blood urea was not of nephritic origin and was not accompanied by urinary disorders or increased blood pressure.

It would appear that in this case there was an isolated plasma hypotonia, because of the blood sodium figure of 130 meq. per liter. The other laboratory findings were only slightly modified.

In summary, a 9-year-old girl was admitted to the hospital on the third day of an attack of cyclic vomiting with ketosis; she had been given small amounts of sodium bicarbonate. She was in coma and displayed Babinski's sign, was without changes in respiration and she vomited unceasingly.

Laboratory findings were chiefly a hypoelectrolytemia, especially a decrease in blood sodium and a very slight change in the chloride and bicarbonate levels.

The ECG tracing was normal. The EEG record showed a somewhat increased number of slow waves.

Sugar and saline solution were given and recovery took place within two days.

In this case, the origin of coma is not clear, as neither acidosis with ketosis nor hypokaliemic alkalosis can account for it. In our opinion, hypoelectrolytemia possibly played a part in its occurrence.

DISCUSSION

The metabolic study of fourteen cases of severe nervous disorders, secondary to attacks of vomiting with ketonuria in children, showed that the changes in the osmotic, acid-base, and electrolytes balance may vary. In eleven patients there was alkalosis with hypochloremia and hypokaliemia, in two acidosis with ketosis, and in one there was an extracellular hypotonia. The clinical picture (Table XIV) resulting from these humoral disorders is often typical enough to permit a differentiation prior to any chemical determination. The analysis of the respiratory pattern is, in our opinion, the most constant element of diagnosis between acidosis with ketosis and alkalosis.

Nevertheless, a chemical study of the blood and urine is necessary for the establishment of the treatment which varies according to the type of the manifestations observed. The predominance of alkalosis is of great importance and most likely related to the present observations. Most attacks of vomiting with ketonuria are treated in France with sodium citrate and bicarbonate and the amounts of these alkaline salts given to the children are often excessive.

Hypochloremic alkalosis with hypokaliemia occurs in many clinical situations: postoperative disease, radiotherapy, postacidotic stage of diabetic acidosis and diarrhea, myocardial infarction, Cushing's disease, DCA, cortisone and ACTH administration. Its occurrence in the course of protracted or intractable vomiting has been seen in adults with various affections: acute intestinal obstruction,[13-18] ulcerous or cancerous pylorus stenosis,[19-21] vomiting of pregnancy.[22] It is also well known in the course of vomiting in infancy, particularly with hypertrophic stenosis of the pylorus.[3, 23-26]

The syndrome can be reproduced experimentally in the animal by diets richer in sodium than in chloride, or

with a potassium-free diet, or by administration of DCA or ACTH, or a combination of these various procedures. Darrow[27, 28] showed that hypochloremic alkalosis and potassium deficiency occurred in close correlation when there is an isolated Cl^- ion or K^+ ion deficiency, without the presence of any other ionic loss or renal insufficiency. The humoral balance that develops in these conditions is characterized in the extracellular fluids by an increase in the pH and bicarbonate level, and by a decrease in chloride and potassium levels; in the intracellular fluids by a decrease in potassium and its replacement by Na^+ and H^+ ions; in the urine, by an increase in the output of Cl, NH_3, K, and H with urinary acidosis. Thus this disorder assumes a double renal and cellular aspect, the respective importance of which is open to discussion. The cellular disorder[39] consists of the shift into the cells of H^+ and Na^+ ions. The renal disorder seems to be due to a competition between K^+ and H^+ in the tubular output. Berliner showed that alkalosis decreases the secretion of K^+ ions in the distal tubules and their replacement by K^+ ions to ensure the exchange of Na^+ ions.[30, 31]

The frequency, severity and often nonrecognized alkalosis with hypokaliemia following attacks of vomiting with ketonuria lead us to stress several points that deserve discussion.

Table XIV. Clinical Symptoms

PATIENT NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
AGE (YEAR)	5	1	6	3	2	2	2	5	7	9	4	6	4	9
Vomiting	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	+	+	+	0	+	+	0	0	0	0
Abdominal pains	+	0	+	+	+	0	0	0	0	0	0	0	+	+
Headache	0	0	0	0	0	0	0	0	0	0	0	0	+	+
Ingestion of CO_3HNa	+	+	+	+	+	+	+	+	+	+	+	0	0	+
Thirst	+	0	+	+	0	+	+	0	+	+	+	+	0	0
Edema	+	0	+	0	0	0	+	0	0	0	0	0	0	0
Dryness of tongue	0	0	0	0	0	0	0	0	0	0	+	+	0	0
Hyperpnea	0	0	0	0	0	0	0	0	0	0	0	+	+	0
Shallow respiration	+	+	0	0	+	+	+	+	0	+	0	0	0	0
Lethargy	+	0	+	+	0	+	0	0	+	0	0	+	0	0
Coma	0	+	0	0	+	0	+	0	0	0	0	0	0	+
Areflexia	+	+	0	0	+	+	+	0	0	0	0	0	0	0
Babinski's plantar reflex	+	0	0	0	+	0	0	0	0	0	0	0	0	+
Hypotonia	+	+	+	0	+	+	+	0	0	0	0	0	0	0
Paralysis	+	+	+	0	+	0	0	0	0	0	0	0	0	0
Chvostek's sign	0	+	0	0	+	0	0	+	+	0	0	0	0	0
Tetany	+	0	0	0	0	0	+	+	+	+	0	0	0	0
Paralytic ileus	+	+	0	+	+	0	+	0	0	0	0	0	0	0
Urinary retention	+	0	0	0	0	0	0	0	0	0	0	+	0	0
Hematuria	+	0	0	0	0	0	0	0	0	0	0	0	0	0
ECG (hypokaliemic)	+	+	+	+	+	+	+	0	0	+	–	–	–	–
EEG (slow waves)	+	+	+	+	+	+	+	+	+	+	–	–	–	0

1. *Physiopathological Mechanism.*—The appearance at times of hypokaliemic alkalosis, despite the existence of a very large ketosis, is an interesting fact. It shows that aceto-acetic acid and betahydroxybutyric acid accumulation, in amounts of nearly 20 acid meq. per liter in some of our observations, is insufficient to balance

the shift to alkalosis induced in such cases by other metabolic disorders. The latter are easily conceived. They are losses in chloride and potassium due to protracted fasting, and to the insufficient carbohydrate metabolism disclosed by ketosis; the violent stress of an attack of intractable vomiting in a child may be an important additional factor through pituitary-adrenal stimulation.

In addition, an analysis of our observations induces us to ascribe an important part to the administration of high doses of sodium bicarbonate for therapeutic purposes. These data were found in all our cases. Because of vomiting, it is difficult to determine accurately the amount of sodium bicarbonate really ingested by our patients. Several investigators studied the action of induced alkalosis. Corda[32] demonstrated the possibility of obtaining definite clinical and biochemical disorders in normal children through experimental administration of sodium bicarbonate. Some studies stress the possibility of significantly increasing the renal excretion of potassium through administration of an alkaline salt; Leaf and associates[33, 34] with sodium citrate; Black and Mills[35] and Greder and Duckert-Maulbetsch[40] with sodium bicarbonate provided convincing data.

Thus, it is likely that the administration of large amounts of sodium bicarbonate in children who, on account of fasting and vomiting, may already display a chloride and potassium deficiency, plays an important part in the precipitation of their disorders.

Case 7 is illustrative: the child, who vomited only moderately, had ingested in three days 180 Gm. of sodium bicarbonate and displayed unusually severe nervous symptoms.

As a consequence, the dangers of an excessive administration of alkaline salts in vomiting, even accompanied with marked ketosis, must be clearly indicated to the general practitioners, particularly in our country.

2. *Special Metabolic Aspects.*—The coexistence of ketosis, with its tendency to acidosis, and of chloride and potassium losses, associated with overdosage of alkaline salts, leads to various considerations discussed in previous papers.[1-3]

(a) *Action of ketosis on hypokaliemic alkalosis:* The existence of ketosis does not necessarily imply an acid deviation of the extracellular pH. The existing electrolytic disorders conceal the accumulation of ketonic acids. The latter should not be considered as chemically toxic; on the contrary, they can be metabolized by many tissues. They are harmful only because they are anions. Their presence in the course of a condition of metabolic alkalosis is not to be feared; on the contrary, it is definitely useful. The comparison of the metabolic course of some of our cases is very instructive in this respect. For instance, in Case 1, the brutal and isolated control of ketosis by the administration of glucose resulted in an immediate aggravation of the alkalosis and hypokaliemia; and the latter was certainly increased by the sudden resumption of carbohydrate metabolism (Fig. 1).

Besides, the large output of ketone bodies may modify the usual syndrome of alkalosis with hypokaliemia. In some of our cases, we could accurately study the urines. In Case 1, the urinary pH was normal, chloruria

was very low at the onset but became normal when the ketonuria disappeared (Table I). In Case 2, the urinary changes assumed two successive aspects: during the first three days, the usual urinary changes of alkalosis with hypokaliemia were found, but chloruria remained low as long as ketonuria lasted. In a latter stage, there was diuresis with large excretion of all elements, and particularly potassium and chloride (Table II).

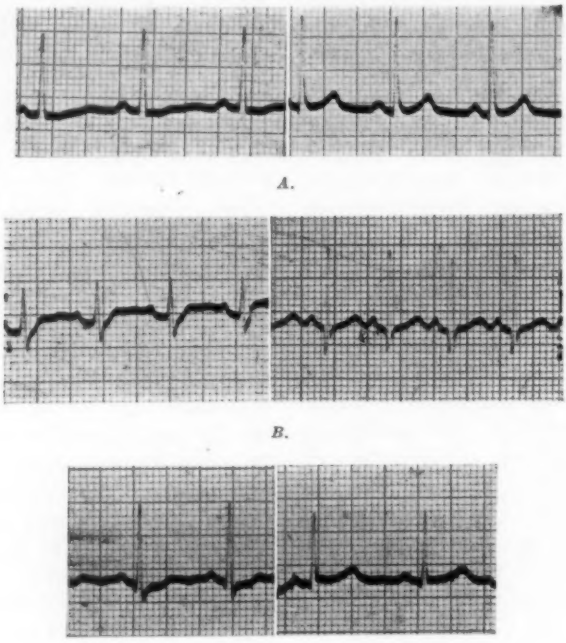


Fig. 14.—Hypokaliemic changes (marked lengthening of Q-T interval; low T wave). Electrocardiograms of *A*, Case 1, on third and sixth days; *B*, Case 2, on second and ninth days; *C*, Case 10, on second and fifth days.

This interpretation, based on the following data, is likely: (1) the massive urinary output of ketonic acids possibly allows a better reabsorption of chloride; (2) the acute dehydration modifies glomerular filtration and the urinary picture during the first days; (3) the early and prolonged administrations of KCl resulted, by the fifth day, in a control of the potassium and chloride deficiency, and in a large output of Cl^- and K^+ in the urine.

(b) *Changes of ketosis due to potassium deficiency:* The production of an excess of ketone bodies in the course of the intermediary fat metabolism is likely to be due to a deficiency in free oxalacetic acid. This deficiency occurs when the cell is lacking in carbohydrates because of insufficient intake, mobilization, or cellular shift. Some experimental findings suggest that carbo-

hydrate metabolism is impaired in conditions of potassium deficiency.[36, 37] This finding possibly accounts for the easy development of hyperglycemia with glycosuria in these patients. It also suggests that the persistance of potassium deficiency may in some cases explain the renewed ketosis in spite of a normal carbohydrate intake (Case 1).

It thus appears that these two co-existing disorders—ketosis and alkalosis with hypokaliemia—may closely affect one another.

(c) *ECG and EEG changes:* We shall not emphasize the ECG changes. We constantly found the usual pattern of hypokaliemia: lengthening of the Q-T interval, flattening and disappearance of the T wave and eventually depressed S-T and appearance of an U wave. These changes disappeared within three to six days with the administration of KCl (Fig. 14).

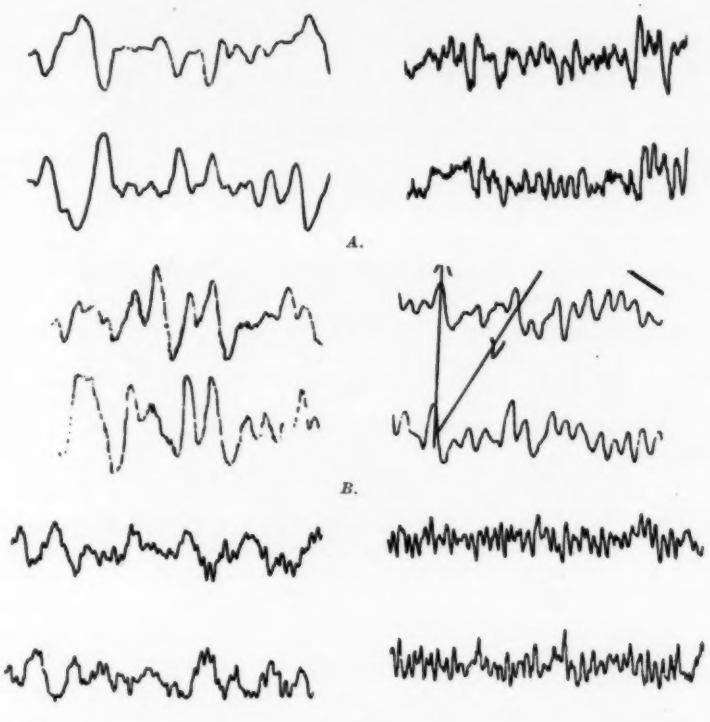
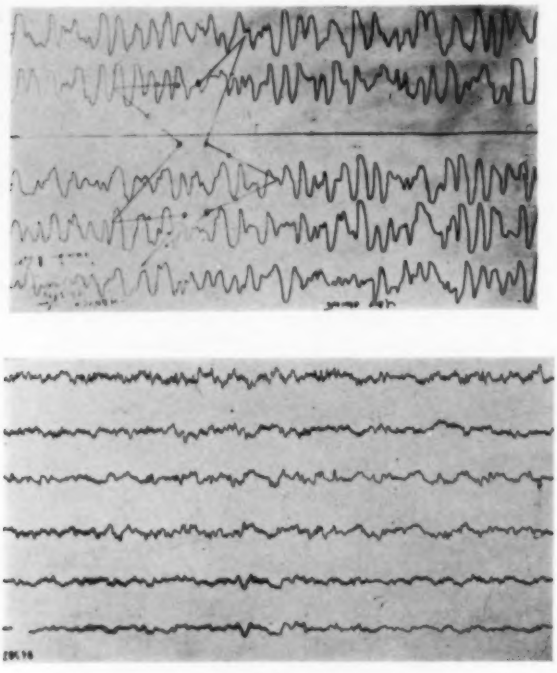


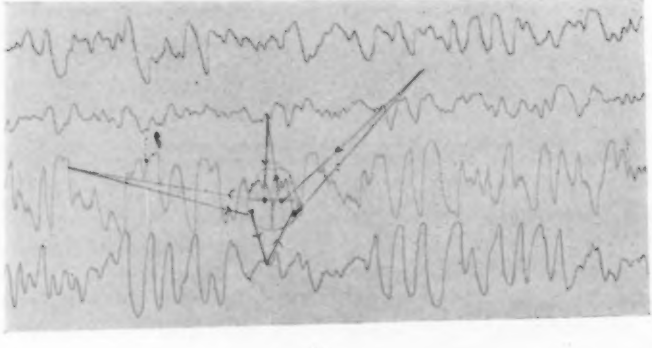
Fig. 15.—Hypokaliemic alcalosis. Electroencephalograms (temporo-occipital) of *A*, Case 1, on first and fifteenth days; *B*, Case 2, on second and ninth days; *C*, Case 10, on third and tenth days.

On the contrary, the study of the EEG pattern is very interesting. We were the first to carry it out in 1953 (Figs. 15 and 16). In ten cases of alkalosis with marked or moderate hypokaliemia, we found significant EEG changes. Tracings recorded in the early stage showed numerous sym-

metric bilateral slow waves, either diffuse or predominating in the anterior or posterior channels. The dysrythmia is impressive and resembles that of diffuse meningoencephalitis. These changes are rapidly controlled and completely disappear when the pH becomes normal, within three to twelve



A.



B.

Fig. 16.—Hypokaliemic alcalosis. Electroencephalograms: *A*, Case 5, on first day, showing dysrhythmia with slow waves, and on third day, showing normal rhythm. *B*, Case 7, on second day, showing dysrhythmia with slow waves.

days. The rapidity of this total return to normal definitely suggests a relationship between these anomalies and the metabolic disorder. The role of the pH increase is probable because the action of gaseous alkalosis on the production of slow waves is well known. A modified hydration of the brain cells may be responsible. On the contrary, nothing substantiates the role of ketosis or of potassium deficiency.

On the other hand, a completely different explanation may be given for the EEG changes. Vahlquist and Nylander[38] recently reported cases of children affected with cyclic vomiting and presenting EEG anomalies. One of their patients already had a disturbed EEG tracing ten days before the onset of an attack of vomiting with ketonuria. In their opinion, cyclic vomiting in this patient was due to a constitutional nervous anomaly, and at autopsy they discovered telangiectases of the hippocampus area. They relate their observations to the "central autonomic dysfunction with defective lacrymation" syndrome described by Riley,[39] a syndrome entailing in some cases cyclic vomiting and EEG changes. Recently Millichap and associates[41] studied thirty-three children in whom a diagnosis of cyclic vomiting was made and their findings support evidence of autonomic epilepsy. The brain disturbance is evident in these cases. But the peculiar recruiting of the children and their history is, in our opinion, more in favor of a particular group of cases than of a real general process. Anyway we remain of the opinion that in our patients the EEG anomalies were related to the metabolic disorders and probably to alkalosis.

THERAPEUTIC CONSEQUENCES

The metabolic symptoms secondary to attacks of vomiting with ketosis in children are varied in nature. Therefore, management must be adjusted to any given case.

Acidosis with ketosis is uncommon; treatment is well known and consists of the administration of 80 to 100 Gm. of water per kilogram per twenty-four hours and of 8 Gm. of sugar per kilogram per twenty-four hours till disappearance of ketosis. In the beginning, a sodium bicarbonate solution is added till cessation of hyperpnea and control of the blood pH. Then, if chloremia and chloruria are decreased, sodium bicarbonate should be replaced by isotonic sodium chloride.

The treatment of alkalosis may vary.

Alkalosis with tetany, or symptom-free hypokaliemia, requires the following measures: administration of 80 to 100 Gm. of water per kilogram per twenty-four hours; of 4 to 5 Gm. of sugar per kilogram per twenty-four hours; the use of calcium chloride and of potassium chloride at a dosage of 1 to 2 Gm. daily. Sodium chloride should be continued at a dosage of 3 to 5 Gm. daily till control of the pH and CO_2 combining power.

Hypokaliemic alkalosis with ketosis dramatically responds to potassium chloride at a dosage of 200 to 400 mg. per kilogram per twenty-four hours.

This medication must be given for five to seven days and discontinued only when food intake is again normal. Clinical symptoms disappear within twenty-four to thirty-six hours, and the ECG and EEG changes within three to twelve days. All of our patients recovered with this treatment,

although some admitted to the hospital were considered in a dying condition.

Eighty to 100 Gm. of water per kilogram per twenty-four hours is given in addition during the first days. Sugar is given in moderate amount, 4 to 5 Gm. per kilogram per twenty-four hours, because, as noted above, there is no importance in too rapid disappearance of ketosis in such cases.

SUMMARY

The metabolic study of fourteen children with severe nervous disorders, secondary to attacks of vomiting with ketonuria, showed that the clinical picture was related once to plasma hypotonia, twice to acidosis with ketosis, and eleven times to hypokaliemic alkalosis.

Thus hypokaliemic alkalosis may coexist with severe ketosis and, in our patients, was the most common cause of the severe symptoms. Its clinical aspect is variable. When hypokaliemia is moderate, tetany due to alkalosis with superficial breathing is common. Under 2.5 meq. per liter, coma or lethargy, muscular hypotonia or flaccid paralysis, edema of the extremities, paralytic ileus, superficial respiration, and urine retention are the clinical features noted. Laboratory determinations confirm pH and bicarbonate increase and the fall of chloride and potassium in blood. The ECG record shows changes related to hypokaliemia. Clinical and biological recovery is achieved within several days under the administration of potassium chloride at a dosage of 200 to 400 mg. per kilogram of body weight daily. The pathogenesis of hypokaliemic alkalosis is complex: digestive loss of chloride and potassium, adrenal cortical stimulation, fasting, and chiefly excessive administration of sodium bicarbonate and citrate in the treatment of the attacks of vomiting with ketosis.

The coexistence of ketosis and of a metabolic alkalosis raises interesting metabolic problems: potassium deficiency may favor the occurrence of ketosis through impairment of carbohydrate metabolism; on the contrary, ketosis modifies the urinary syndrome of hypokaliemic alkalosis and is useful to a point because it balances a partial alkalosis by anions.

The EEG study of children with hypokaliemic alkalosis and ketosis shows impressive diffuse and symmetric slow waves which disappear, with a short lag, when the metabolic disorders are controlled. These EEG changes are likely to be directly related to alkalosis and impaired hydration of the brain cells. From the practical viewpoint, the relative frequency of hypokaliemic alkalosis in the course of the nervous disorders, secondary to vomiting with ketosis, in contrast to the uncommon occurrence of ketoacidosis, leads to a cautious establishment of the therapeutic measures. The best clinical sign of diagnostic value is the type of the respiration: superficial respiration in alkalosis, hyperpnea in acidosis with ketosis.

Nevertheless, chemical determinations, ECG and EEG records are necessary to establish the type and degree of the electrolyte and acid-base imbalance and the management to be used: sodium bicarbonate in acidosis, potassium chloride in hypokaliemic alkalosis.

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THE PROBABILITY OF DETECTING INFECTIONS WITH ENTEROBIUS VERMICULARIS BY SUCCESSIVE EXAMINATIONS

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THE use of the cellulose tape slide preparation for the laboratory diagnosis of infections with *Enterobius vermicularis* has attained widespread acceptance. However, in view of variables such as numbers of worms present, numbers of migrating females, and days on which they migrate or fail to migrate, it is generally admitted that a significant percentage of infections are missed by a single examination, even with this technique. A preliminary estimation of the value of repeated examinations by the use of the NIH swab[1] was made by Cram and her co-workers.[2] However, their results were affected by the fact that they used information obtained from preparations collected at different times of day, with different periods of time elapsing between examinations, and examined by different persons. To our knowledge no information is available in the literature which indicates the percentage of infections revealed by a single cellulose tape preparation, and the minimal number of successive examinations necessary for reliable and comparable results.

During the course of chemotherapeutic studies at a Florida mental institution, we had occasion to perform successive daily examinations on a large series of patients in an effort to determine, before treatment, the prevalence rate of infection with this nematode. The findings of those examinations form the basis of this report.

From the Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare, Atlanta, Ga.

MATERIALS AND METHODS

Six consecutive cellulose tape preparations were examined for each of 307 persons in nine wards in order to estimate the cumulative probabilities of detecting infections by successive examinations. The cellulose tape slides were prepared and used following, essentially, the technique described by Brooke and co-workers.[3] All the specimens were collected by the same person at night between 9 P.M. and midnight. The nurse collecting the tapes washed her hands thoroughly at regular intervals in order to minimize the danger of transferring eggs from tape to tape by contaminated fingers. In the laboratory, the preparations were examined with a 16 mm. objective and 5X oculars after a drop of toluene had been placed under the tape.[4] The entire preparation was examined. The complete examination of each slide required about fifteen minutes. This is longer than the time which would be needed if only that portion of the tape which touched the patient was observed under the microscope, as recommended by previous

authors. However, preliminary observations indicated that in a significant number of patients only a few eggs in a marginal position could be missed if a portion of the tape was examined.

RESULTS AND DISCUSSION

The results of 1,842 examinations performed on 307 patients are summarized in Table I. The prevalence rate based on six consecutive examinations for the entire group was 67 per cent. If only a single examination had been used, the prevalence rate would have been between 25 and 37 per cent. No significant difference was encountered between the prevalence in any one day and the following day. However, the difference between the per cent positives found on the first two days (thirty-seven) and on the fourth day (twenty-five) is statistically significant at the 5 per cent probability level. No definite explanation can be offered at the present time for such observation. It is possible that as the experiment progressed, the attention of the patients might have been focused on the perianal region with a consequent increase of local hygiene and/or scratching. Either of these actions would cause some eggs to be dispersed before the specimens were obtained. With the first examination, 55 per cent of the positives found as a result of six consecutive specimens was detected. The probabilities of demonstrating infection increased somewhat regularly with each successive examination. After the third examination, eggs had been found in one or more specimens of 185 out of 206 infected patients, or 90 per cent of the estimated infected population.

Breakdown of the data, by individual buildings from which the specimens were taken, indicates differences in prevalence rates of this infection from building to building. Relatively speaking, the prevalence was light in three wards and heavy in six wards. The observed differences from building to building are partially accounted for by differences in the age groups of the patients, by the severity of their mental illness, and by the regimen of treatment of their mental conditions. It is realized that the efficiency figures of consecutive examinations in a heavily infected group of individuals are not necessarily valid for other population groups where the prevalence rate is significantly lower. Therefore, the data obtained in the wards with the lower prevalence rates are tabulated separately from those obtained in wards with higher prevalence rates.

In three buildings, forty-three out of 104 patients, or 41 per cent, were found infected with *E. vermicularis*

TABLE I. RESULTS OF CONSECUTIVE EXAMINATIONS FOR E. VERMICULARIS OF 307 PERSONS IN NINE BUILDINGS

SPECIMENS	POSITIVES AT EACH EXAMINATION		CUMULATIVE TOTAL		PER CENT OF PREVALENCE BASED ON SIX SPECIMENS
	NUMBER	PER CENT	NUMBER	PER CENT	
1	113	37	113	37	55
2	113	37	159	52	77
3	96	31	185	60	90
4	78	25	196	64	95
5	86	28	203	66	99
6	81	26	206	67	100

(Table II). The prevalence rate determined by a single examination varied from 12 to 21 per cent. With the first examination, only 37 per cent of the positives found as a result of six consecutive specimens was detected. After the third examination, eggs had been found in thirty-nine out of forty-three positives, or 91 per cent of the infected population.

In six wards, 163 out of 203 patients, or 80 per cent, were found infected with this nematode (Table III). Whether these occasional eggs in marginal positions were due to displacement after the introduction of toluene, to accidental contamination, or to both, could not be determined at the present time. However, in view of the precautions taken in the collection of specimens, it is unlikely that accidental contamination played a major role.

A comparison of the results, summarized in Tables II and III, indicates that although a lower efficiency

TABLE II. RESULTS OF CONSECUTIVE EXAMINATIONS FOR E. VERMICULARIS OF 104 PERSONS IN THREE BUILDINGS WITH A RELATIVELY LOW PREVALENCE

SPECIMENS	POSITIVES AT EACH EXAMINATION		CUMULATIVE TOTAL		PER CENT OF PREVALENCE BASED ON SIX SPECIMENS
	NUMBER	PER CENT	NUMBER	PER CENT	
1	16	15	16	15	37
2	22	21	29	28	67
3	19	18	39	37	91
4	12	12	41	39	95
5	14	13	43	41	100
6	12	12	43	41	100

TABLE III. RESULTS OF CONSECUTIVE EXAMINATIONS FOR E. VERMICULARIS OF 203 PERSONS IN SIX BUILDINGS WITH A RELATIVELY HIGH PREVALENCE

SPECIMENS	POSITIVES AT EACH EXAMINATION		CUMULATIVE TOTAL		PER CENT OF PREVALENCE BASED ON SIX SPECIMENS
	NUMBER	PER CENT	NUMBER	PER CENT	
1	97	48	97	48	60
2	91	45	130	64	80
3	77	38	146	72	90
4	66	33	155	76	95
5	72	35	160	79	98
6	69	34	163	80	100

The prevalence rate, determined by a single examination, varied from 33 to 48 per cent. Sixty per cent of the positives were detected by the first examination. After the third examination, eggs had been found in 146 out of 163, or 90 per cent, of the estimated infected population.

It should be noted that about 40 per cent of the cellulose tape preparations contained 5 eggs, or less, and that many of these eggs were found in a marginal position on the slide. in demonstrating infections by single examinations is obtained among population groups with a lower prevalence, after the third consecutive examination the cumulative probabilities of detecting infections are equivalent.

The results, in general, indicate that a system of examining a single specimen does not give figures on which calculations of the true incidence of the infection can be based and that such figures are not comparable if derived from varying kinds of popula-

tions with different prevalence rates. It seems probable, however, that a system of six consecutive examinations would reveal a fairly constant proportion of the actual infections and that with this number of examinations practically all of the existing infections are revealed. If, for reasons of economy of time and/or lack of daily contact with noninstitutionalized patients, it is impractical to perform six examinations on a person, the results indicate that three specimens may be sufficient to reveal most of the actual infections. The differences in demonstrability in population groups with varying incidences and degrees of intensity of infections may be expected to have largely disappeared after the third examination and the results, consequently, be directly comparable.

SUMMARY

A total of 1,842 cellulose tape preparations were collected on six consecutive days from 307 patients in a mental institution. The findings indicate that a single examination is not reliable for the detection of infections with *Enterobius vermicularis*. A lower efficiency in demonstrating infections by single examinations was obtained among groups with a lower prevalence. The differences in demonstrability in groups with varying incidences and intensities of infection largely disappeared after the third daily examination and the results, consequently, were directly comparable. It is believed that a system of six consecutive examinations reveals a high and consistent proportion of the existing infections.

The authors wish to express their appreciation to Dr. C. H. Carter, Medical Officer in Charge, Florida Farm Colony, Gainesville, Florida, for his interest and cooperation.

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DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS IN CHILDREN

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PULMONARY fibrosis is a pathologic state which occurs in a variety of conditions and is found in a number of different forms. It is perhaps most frequently associated with chronic pulmonary emphysema[1] and as such is a rather familiar disease state. Other diseases which are often associated with or characterized by pulmonary fibrosis include tuberculosis, Boeck's sarcoid, and the other pulmonary granulomatoses, as well as scleroderma and various types of bacterial pneumonia. In view of this varied etiology, attempts have been made to classify the condition on a pathologic or physiologic basis, none of which has been pre-eminently satisfactory. In this paper our interest will be directed toward a form of pulmonary fibrosis which, in the ten years since its original description, has come to be known as idiopathic diffuse interstitial fibrosis of the lungs.

In 1944, Hamman and Rich[2] first described this condition as an acute process involving a rapidly progressing fibrosis of the interalveolar septa, with little or no exudative reaction. Literature on the subject was slow to accumulate, and the condition became known as the "Hamman-Rich syndrome." Since 1950, however, there has been renewed interest in the problem, and several authors have reported original cases with reviews of the existing literature. Rubin and associates[3] reported one case, with a review of the problem, and suggested that etiological factors might include: (1) influenzal pneumonia or chemical irritants (Hamman and Rich); (2) "acute interstitial pneumonia" (Golden and Tullis); or (3) other bizarre pneumonias such as that associated with scrub typhus and the other rickettsial diseases. Callahan and his group,[4] in a similar report, brought out the fact that the disease often pursued a markedly chronic course, some cases progressing for seven years before death. They also re-emphasized the predominance of right ventricular dilatation as an accompaniment of the disease (chronic cor pulmonale) even though some reported cases showed dilatation of the left atrium. The lack of cellular infiltration in post-mortem histologic studies of the lungs brought these authors to the conclusion that the condition was either of noninflammatory, chemical, or viral origin. Golden and Bronk[5] presented another three cases and came to the conclusion, through the use of newer pathologic techniques, that the characteristic pathologic process was one of "progressive diffuse alveolar hypertrophy of a specific reticulo-angiotic type"; that is,

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The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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alveolar wall hypertrophy in their specimens was shown to be due to considerable capillary proliferation. They also emphasized the chronicity of the disease.

There had been some twenty-five typical cases, as well as twenty less typical instances of the disease reported by 1954. The prevailing opinions of various investigators were summarized by Clough[6] who emphasized the fact that symptoms were usually somewhat prolonged and included vague periods of ill health, chronic cough, and mild dyspnea. Mild intercurrent respiratory infections were not uncommonly a part of the picture and seemed to accelerate the course of the disease. Positive diagnosis has been shown to depend on histologic examination, and is usually made at autopsy. Pathologic processes include an early swelling and edema of the alveolar walls, together with a deposition of fibrin. There is usually a moderate infiltration of mononuclear cells and eosinophils, and a concomitant or subsequent proliferation of young fibroblasts within the alveolar septa. There may or may not be hyaline membrane formation. Secondary features which are often found include subintimal thickening of the arterioles, peribronchiolar fibrosis, and the formation of tiny emphysematous blebs.

It is also known that symptoms referable to the cardiovascular system are a frequent early and terminal accompaniment of diffuse interstitial pulmonary fibrosis.[7] These symptoms usually are manifestations of a slowly progressive cor pulmonale. Acute cor pulmonale is rarely, if ever, associated with this disease.[8] While clinically and electrocardiographically[9] the cardiac abnormalities seem to represent a "typical" cor pulmonale, a mass of data compiled and critically evaluated by Cournand and his co-workers shows that cardiopulmonary dysfunction in this disease is not exactly similar to that associated with the usual case of cor pulmonale. West and associates[10] characterized those diseases (such as diffuse interstitial fibrosis) with "impairment of alveolar-capillary diffusion," as showing a decreased oxygen-diffusing capacity, an increase in the "physiologic dead space" (i.e., adequate ventilation of poorly perfused alveoli), and an increase in the "physiologic venous admixture" (i.e., adequate perfusion of poorly ventilated alveoli). Harvey and co-workers[11] showed that patients with chronic pulmonary disease, characterized by what they called "diffusion fibrosis" (resulting in impaired alveolar-capillary diffusion), also showed a pulmonary hypertension at rest as well as a considerable increase in cardiac output. It was thought by these authors that the former was due to an anatomic reduction of the capacity of the pulmonary bed, but no suitable explanation could be found for the latter. Shortly afterward, Austrian and associates[12] presented evidence that the pulmonary dysfunction in cases of diffuse interstitial fibrosis was manifested as: (1) reduced lung volumes; (2) maintenance of a large maximum breathing capacity; (3) hyperventilation at rest and during exercise; (4) normal or near normal arterial oxygen saturation at rest, with a distinct reduction in this value following exercise; (5) normal alveolar oxygen tension; (6) reduced oxygen-diffusing capacity; and (7) pulmonary artery hypertension. This set of circumstances was thought to be best represented by the term "alveolar-

capillary block." Diseases characterized by these conditions included: (1) pulmonary granulomatoses, (2) Boeck's sarcoid, (3) scleroderma, and (4) diffuse interstitial pulmonary fibrosis, all of which diseases have a similar pulmonary involvement.

In contrast to these findings Fowler and his group[13] have reported that most cases of chronic cor pulmonale in association with chronic lung disease show a normal or low cardiac output with a normal pulmonary mean pressure. Other observers have found increased pulmonary pressure[6] in these diseases. Another interesting unsolved problem concerns the physiologic abnormalities responsible for the left ventricular hypertrophy and/or dilatation which is not infrequently seen in cases of chronic cor pulmonale,[14] and which has been observed also in the pathogenesis of diffuse interstitial pulmonary fibrosis.[4] Those cases of left ventricular enlargement developing in the course of cor pulmonale secondary to tuberculosis and chronic emphysema have been attributed to anoxia; perhaps low arterial oxygen saturations and an increased cardiac output can account for the increase in size of the left ventricle in cases of diffuse interstitial pulmonary fibrosis. It is also interesting to note that three cases demonstrating a marked clinical similarity to reported cases of diffuse fibrosis have been reported[15] as being due to "primary pulmonary hypertension" with the pathologic picture of pure pulmonary arteriosclerosis and no fibrosis of the alveolar septa.

Treatment of these patients generally has been disappointing, with gradual but relentless progression of cardiopulmonary failure and eventual death. There have been some instances of gratifying improvement in patients treated with cortisone.[10, 16] Unfortunately, there has been an equal number of failures with this therapy.[7, 16]

It is significant in our discussion that of the approximately forty-five cases reported there have been no instances of the disease in children; the age range has been from the second to the eighth decade.[2-7, 10-12, 16, 17] Maxwell and Wilson,[18] as well as De Muralt and Menano,[19] have discussed the problem of cor pulmonale in infants; in neither of these studies has the presence of diffuse interstitial pulmonary fibrosis been mentioned.

CASE REPORT

The following is a case report of a child whose clinical course was suggestive of many pathologic processes, but whose post-mortem histologic findings were typical of diffuse interstitial fibrosis of the lungs.

The patient, a white female, was born on March 24, 1945, following a normal full-term pregnancy. Delivery was normal and spontaneous, the birth weight was approximately 7 pounds, and there were no neonatal complications. Growth and development were normal and the diet was adequate. She was immunized with D.P.T. and cowpox vaccine. She had an episode of "strep throat" at 16 months which required hospitalization for several days and treatment with antibiotics. At the age of 6 she was hospitalized for acute, nonparalytic, anterior poliomyelitis; no residua were ever demonstrated. There was no history of allergy or drug reactions. The family history was noncontributory.

The patient's first complaint of a cardiorespiratory nature was noted on May 20, 1952, nine months after the episode of poliomyelitis. At this time she developed symptoms of an upper respiratory infection and was treated at the pediatric clinic of another hos-

pital with both penicillin and broad spectrum antibiotics. There was radiologic evidence of a right basilar pneumonitis and a "suggestion" of left ventricular enlargement. She became symptom-free within a week.

She next sought medical care on Dec. 4, 1952, after having had a cough for twenty days. A diagnosis of acute bronchitis was made and the child was given 600,000 units of penicillin over the next two days and was not seen again until a week later, at which time her mother stated that she had had a fever and had been short of breath for the previous three days. Physical examination at this time revealed an evident pallor and obvious cardiac decompensation. The patient was acyanotic; blood pressure was 110/78; the liver edge was palpable 2 cm. below the right costal margin and there was a 2+ pitting pedal edema. The child was admitted to the hospital with the diagnosis "acute interstitial nephritis" on the basis of an acid urine containing 100 mg. of albumin with 8 to 10 white blood cells per high dry field and a few epithelial cells; there were no casts in the urinary sediment. Digitalization was begun on the following day when there were basilar râles bilaterally and the liver edge was down 10 cm. She was treated with the usual measures for cardiac decompensation. The urine cleared in three days and no abnormalities were subsequently found. There was no evidence of manual or periorbital edema or anasarca. The blood pressure remained at normal levels. X-ray of the chest during this hospitalization was reported as showing "cardiac dilatation." An electrocardiogram taken on the fourth hospital day showed right axis deviation and a suggestion of left ventricular strain in an abnormally vertical heart. There was evidence also of auricular enlargement. The patient's condition gradually improved, digitalis was discontinued on the fourth hospital day, and she was discharged on the twelfth. Three follow-up visits to the pediatric clinic at that hospital showed the urine to be normal, and the patient to be free of symptoms. Chest x-ray five weeks after admission to the hospital showed some equivocal residual cardiac enlargement.

On Feb. 17, 1953, approximately two months after the onset of her previous episode, the patient was brought to the pediatric clinic at this hospital. The chief complaint was given as "heart failure"; following discharge from the previous hospitalization she had complained of exertional dyspnea, easy fatigability, paleness, and had lost 6 pounds in weight. Physical examination showed a chronically ill child with distended cervical veins and a precordial bulge. The heart was enlarged to palpation, the point of maximum intensity being displaced laterally to the anterior axillary line. There was a harsh systolic murmur along the left sternal border heard in inspiration only. A_2 was greater than P_2; the latter was snapping. The blood pressure was 106/60. The liver was palpable two fingerbreadths below the right costal margin. The skin was dry and scaly. She was admitted to the hospital with the provisional diagnoses of acute rheumatic carditis and ichthyosis, and an extensive workup was begun.

Repeat hemograms showed the patient to be mildly anemic; urinalysis on several occasions showed albuminuria and microscopic hematuria which were felt to result from cardiac decompensation. Serologic tests for syphilis, skin tests with tuberculin and coccidioidin, blood urea nitrogen, total protein, and A/G ratio were all normal. The antistreptolysin titer was reported as 166 or greater. Repeated electrocardiograms showed left ventricular enlargement in a vertical heart and auricular hypertrophy. X-ray examination including oblique views and barium swallow showed marked enlargement of the left auricle and ventricle with no significant pulmonary congestion, and no abnormality of the hilar pulsations.

Digitalization resulted in definite continued improvement of the patient's condition, and also caused a change in auscultatory observations. The systolic murmur previously described decreased in intensity while a diastolic murmur, previously not heard, was elicited over the apex. P_2 became louder than A_2. A pediatric consultant felt that electrocardiograms showed right ventricular enlargement as well as the previously mentioned abnormalities and advised cardiac catheterization for definitive diagnosis, feeling that the most likely diagnostic possibilities were: (1) interatrial septal defect and (2) "primary pulmonary sclerosis." Cardiac catheterization was performed on May 12, 1953, by the cardiac laboratory of the University of California; pertinent portions of the report of this procedure are quoted. "Intracardiac and pulmonary artery pressures were at the upper limits of normal or slightly elevated. No abnormal vessels or septal defects were entered. . . . In conclusion, these findings may be within normal limits. . . . There is insufficient evidence of anatomic abnormality to account for the history of congestive failure. It was the conclusion of the group that the patient had probably had some kind of myocarditis. . . ."

The patient was followed for the next several months in the pediatric clinic. She was maintained on varying doses of digitoxin; this drug was omitted for one month when the child was thought to be doing well, but reappearance of signs and symptoms of mild failure prompted its reinstitution. During the months from May, 1953, to June, 1954, she had a number of episodes of fever, cough, and dyspnea which were diagnosed as bronchitis and bronchiolitis. She was treated with a variety of broad spectrum antibiotics with a variety of results. While she was receiving digitoxin there was no evidence of cardiac failure. Electrocardiograms taken during this time were interpreted as showing increasingly marked right ventricular hypertrophy as well as right auricular enlargement. V_{3R} leads were taken to substantiate these observations. Roentgenographically, the cardiac configuration was not observed to change.

It became the concensus among her physicians that the patient's difficulty was based on an idiopathic pulmonary hypertension and it was decided to prescribe a trial course of cortisone. This was prevented by the appearance of a right pleural effusion associated with bronchitis and recurrence of cardiac decompensation. She was treated with bed rest and vigorous doses of antibiotics; no improvement was noted, however, and in spite of continued treatment the pleural effusion became more marked and cardiac decompensation gradually brought about an increase in the pulse to 110, severe dyspnea, and a 4+ pitting edema of the legs.

Accordingly she was readmitted to the hospital on July 13, 1954, and in spite of the extreme decompensation and marked anemia 200 mg. of cortisone was given daily. Small infusions of packed cells were given for the anemia and the dosage of digitoxin was increased. Electrocardiograms continued to show marked right ventricular and auricular hypertrophy; chest x-ray demonstrated persistance of the pleural fluid with no obvious change in the cardiac silhouette. Considerable improvement in the patient's subjective condition followed institution of the therapeutic measures mentioned; however, on July 31, 1954, she complained of an extreme increase in shortness of breath and examination revealed an acute, severe exacerbation of cardiac decompensation. In the face of sedation, mercurials, and aminophylline her condition steadily disintegrated and within twelve hours she was dead.

At autopsy the following observations were made. Examination of the thoracic cavity showed bilateral pleural effusion with numerous pleural

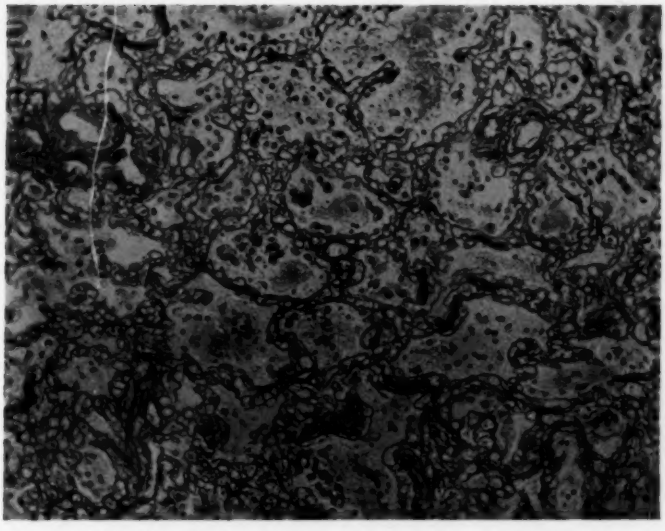

Fig. 1.—Fibrous thickening of the alveolar septa. (Masson stain; ×160; reduced ⅙.) (Courtesy Armed Forces Institute of Pathology, Washington, D. C.)

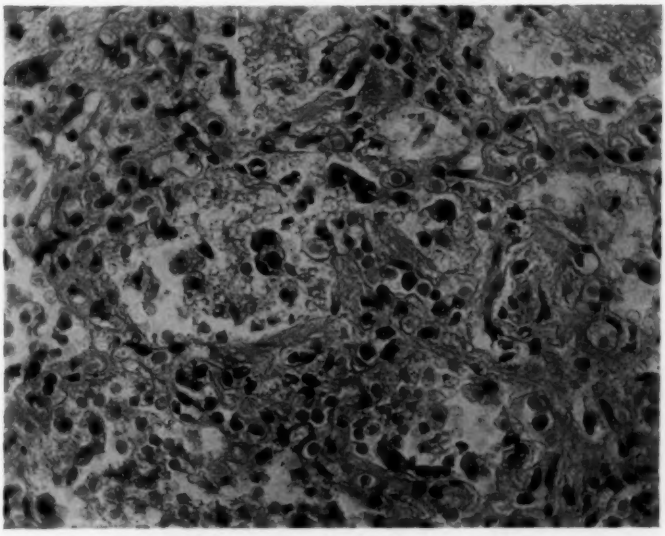

Fig. 2.—Fibrous thickening of the alveolar septa. (H & E; ×420; reduced ⅙.) (Courtesy Armed Forces Institute of Pathology, Washington, D. C.)

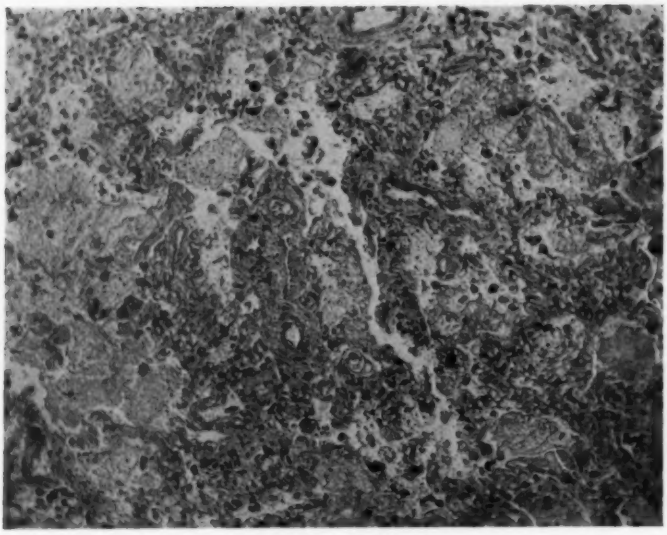

Fig. 3.—Small vessels showing no abnormality other than some adventitial thickening. (H & E; ×135; reduced ⅙.) (Courtesy Armed Forces Institute of Pathology, Washington, D. C.)

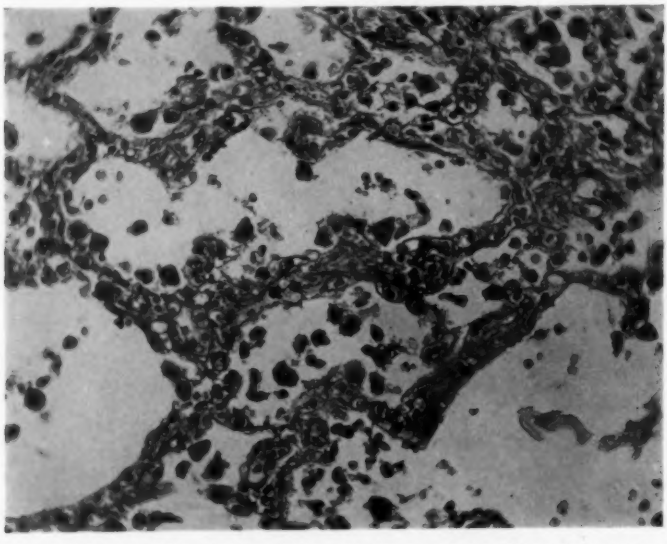

Fig. 4.—Moderate fibrosis of the alveolar septa. (Masson stain; ×280; reduced ⅙.) (Courtesy Armed Forces Institute of Pathology, Washington, D. C.)

adhesions, and dense pleuropericardial adhesions. The lungs were of a solid liverlike consistency, and showed four areas of infarction, three being in the left upper lobe with one in the right lower lobe. The pulmonary vessels were normal. The alveoli were either collapsed or showed a fibrillar light pink-staining material within their cavities. These latter alveoli showed numerous pigment-bearing macrophages. The alveolar septa were thickened and were infiltrated with round cells predominantly, with occasional polymorphonuclear leukocytes. The infarcted areas were of the same microscopic pattern as described above except for extensive extravasation of red cells into the alveoli.

The heart weighed 330 grams and there was hypertrophy and dilatation of all chambers. The average thicknesses of the left and right ventricular walls were 12 and 6 mm., respectively. There were no other gross or microscopic cardiac abnormalities. The liver was enlarged and showed evidences of early passive congestion. There was an incidental Meckel's diverticulum. The final pathologic diagnoses were:

1. Chronic diffuse bilateral pneumonitis with acute exacerbation, and bilateral pulmonary fibrosis.
2. Pulmonary edema, bilateral.
3. Cardiac hypertrophy.
4. Pleural effusion, bilateral.
5. Meckel's diverticulum.

Microscopic sections of the lungs were reviewed by the Armed Forces Institute of Pathology and it was felt[20] that the small pulmonary arteries and precapillary vessels were essentially normal. There was adventitial thickening in some areas but this seemed to be more a product of the diffuse fibrosis rather than a specific vascular abnormality. There was no endothelial swelling or degeneration of the walls of the vessels.

DISCUSSION

In spite of the atypical clinical course of this patient's disease it is believed that the post-mortem histologic observations justify the diagnosis of diffuse interstitial pulmonary fibrosis. It is significant that the almost exclusively mononuclear infiltration was found only in the alveolar septa, along with fibrosis of these areas. The presence of an acute exacerbation of pneumonitis is doubted because of the paucity of polymorphonuclear cells and the lack of an exudate in the alveoli themselves, which were filled only with an eosinophilic-staining material and "heart failure cells."

Clough[6] has stated that a history of antecedent pneumonia is the exception rather than the rule in patients with this disease; several authors[3] have suggested, however, that the condition may be due to inflammatory processes of a viral, chemical, or rickettsial nature. The place of pneumonia, or rather pneumonitis, in the pathogenesis of diffuse fibrosis has not been accurately evaluated as yet. Perhaps the most astute statement as to the etiology of the condition was made by Silverman and Talbot[7] who believed it to be "probably a syndrome produced or initiated by a variety of agents." The episodes of pneumonitis, bronchiolitis, and bronchitis in this patient's disease do not lend themselves to easy interpretation. The terminal episodes seem more likely to be secondary to her previously existing cardiac decompensation. Whether or not the initial pneumonitis was active etiologically is as significant as it is unanswerable. It can be said, however, that these early infections were not typically bacterial in view of their unsatisfactory response to the usual antibiotics.

The pattern of cardiac involvement in this patient is difficult if not im-

possible to explain rationally. Involvement of the left side of the heart as an early feature of this disease is not reported in the literature. Speculation as to the reasons behind this bizarre picture would be fruitless. The possible role of anoxia and high cardiac output in cor pulmonale and in the "alveolar-capillary block syndrome" as a cause of left ventricular enlargement already has been presented. The presence of a bizarre myocarditis and pneumonitis as primary etiological agents is an intriguing possibility which, however, is not supported by the pathologic sections of the myocardium and the lung.

SUMMARY AND CONCLUSION

A case of diffuse interstitial pulmonary fibrosis in a female child has been presented and the pertinent literature reviewed. The physiologic and pathologic characteristics of the disease have been fairly precisely described but the etiology remains a matter of speculation.

The many atypical features of the case presented and the futility of the therapeutic measures employed emphasize the need for further investigation of this disease in children.

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STREPTOCOCCAL DISEASE IN SOUTHERN CALIFORNIA

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RECENT reports have emphasized the importance of β hemolytic streptococcal disease in the etiology of rheumatic fever.[1, 2] The role of environment in potentiating streptococcal disease and/or rheumatic fever is less clear, however. Conflicting statements have appeared regarding the incidence of both streptococcal disease and rheumatic fever throughout the United States and also various parts of the world.[3, 4] However, it is the general impression of some physicians that rheumatic fever is less common in the milder climates.

Since it would appear from certain studies that rheumatic fever is a sequela in 3 to 4 per cent of streptococcal infections, a pertinent question would be, Does the incidence of streptococcal disease vary significantly throughout the United States? Recently, Breese and Disney[5] have indicated that streptococcal disease can be diagnosed with a high degree of accuracy in children particularly over the age of 5 years. If such is possible, data regarding the incidence of streptococcal disease might have more significance, particularly as they would relate to the incidence of rheumatic fever.

The first part of this study was undertaken in an effort to substantiate the observations of Breese and Disney, and also to obtain some information for ourselves regarding the incidence of streptococcal disease and the streptococcal carrier state in a general pediatric clinic in Southern California. Additional information was collected from certain city health department reports in an effort to compare the incidence of reported streptococcal disease in cities from various parts of the United States.*

METHODS

All the children seen at the Marion Davies Children's Clinic of the University of California at Los Angeles for a six-week period beginning July 15, 1954, had a throat culture taken. The cultures were taken in a routine manner, by passing a cotton swab over the anterior pillars or tonsils. They were then plated on blood agar immediately. The plates were read in twenty-four hours and suspicious colonies were isolated and studied microscopically. Data regarding the age, sex, and occurrence of rheumatic fever in the family were obtained on all the children. During the same period certain blood acute phase reactant studies were done at random on

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children symptom free from respiratory disease.

Children with symptoms of respiratory disease were seen by one of us (A. T.) and data concerning fever, vomiting, rash, and the appearance of the throat were recorded. The examiner then indicated whether the infection had the appearance of streptococcal disease.

The study was repeated again beginning Feb. 7, 1955, for a one-month period. The same procedure was used this time as was used the first.

RESULTS

Table I summarizes the results of the clinical and culture studies for the two periods: Summer, 1954, and Winter, 1955. A total of 569 patients was studied in the summer period and 404 in the winter period. The sex distribution was not remarkable. The age range and the mean age were ap-

TABLE I. SUMMARY OF CLINICAL AND CULTURE STUDIES FOR THE TWO PERIODS

	SUMMER (1954)	WINTER (1955)
Total number of patients	569	404
Males	313	199
Females	256	205
Age range	1 mo. to 17 yr.	1 mo. to 15 yr.
Mean age	5+ years	6 yr.
Asymptomatic	539	369
Streptococci cultured	10 (2%)	24 (6%)
Family History of R. F.	68 (12%)	61 (15%)
Sore throat	30	35
Males	17	17
Females	13	18
Number diagnosed as streptococcal	0	4*
Number streptococci cultured	1 (3%)	6† (18%)

*Two of these did not culture out streptococci.
†Four of these were not thought to have streptococcal disease.

TABLE II. SYMPTOMS AND FINDINGS OF THIRTY-FIVE CHILDREN WITH SORE THROAT DURING THE WINTER PERIOD 1955

	STREPTOCOCCI CULTURED	STREPTOCOCCI NOT CULTURED
Total number of patients	6	29
Headache	3	1
Abdominal pain	2	3
Vomiting	0	6
Chills	1	1
Cough	5	22
Hoarseness	1	6
Fever	3	11
Pharyngitis		
1+	3	20
2+	2	5
3+	1	4
Petechiae in throat	-	1
Scarlet rash	1	1
Cervical adenitis	3	4

TABLE III. INCIDENCE OF STREPTOCOCCOSIS PER 100,000 POPULATION

YEAR	NEW YORK	LOS ANGELES	SALT LAKE	CHICAGO
1930	110	144	139	287
1931	170	81	98	242
1932	297	144	97	223
1933	115	156	148	259
1934	123	182	345	290
1935	201	156		490
1936	156	179		229
1937	137	94		236
1938	113	110		215
1939	82	135		190
1940	181	79		376
1941	96	68		151
1942	96	56		87
1943	128	60	347	78
1944	118	74	509	137
1945	113	118	173	116
1946	107	98	143	74
1947	48	55		39
1948	32	37		46
1949	29	31		37
1950	21	30		21
1951	28	51		30
1952	45	33		42
1953	22	39		43
1954	27	32		37

proximately the same for both periods: 1 month to 17 years with a mean of 5+ in the summer and 1 month to 15 years with a mean of 6 in the winter.

Of the 539 who were asymptomatic in the summer period, streptococci were cultured in ten (2 per cent). In the winter, streptococci were cultured in twenty-four (6 per cent) of 369 asymptomatic children. The incidence of a positive family history for rheumatic fever in the total group for both summer (12 per cent) and winter (15 per cent) was essentially the same.

In the summer period, thirty children complained of sore throat; none of these were thought clinically to be due to streptococci but in one patient streptococci were cultured. In the winter period thirty-five children complained of sore throat, four of these were thought clinically to be due to streptococci, but in two none were cultured. In the six in whom streptococci were cultured, four were not thought clinically to have streptococcal disease.

Table II summarizes the symptoms and physical findings of the thirty-five children who complained of sore throat in the winter period of 1955. Analysis of this table reveals that cough, fever, and pharyngitis were about equally common to both groups. The main difference in the two groups was the higher incidence of vomiting and hoarseness in those in whom streptococci *were not* isolated.

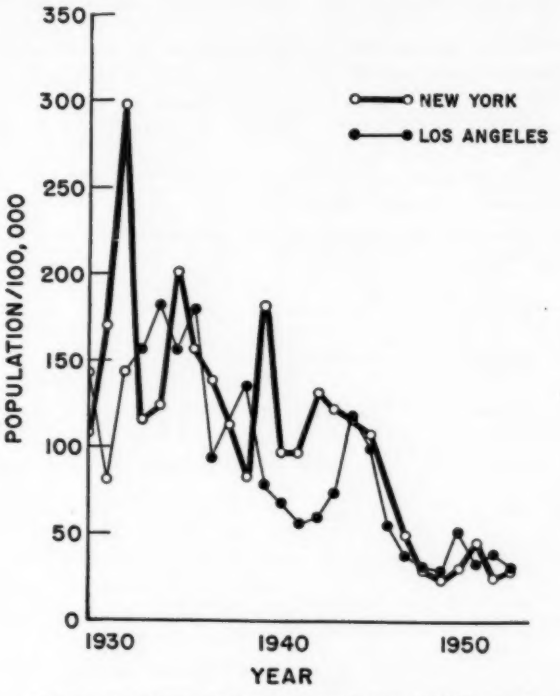

Fig. 1.—Incidence of streptococcosis per 100,000 population.

None of the patients with streptococcal disease developed rheumatic fever during the course of the study. All patients received therapeutic amounts of penicillin for seven to ten days either by mouth or injection.

Table III summarizes the data collected from the available city health department reports for the period 1930 to 1954 for the following cities: New York, Chicago, Salt Lake City, and Los Angeles. The incidence rates are expressed as the number of streptococcal cases per 100,000 population in order to make the data comparable. Except for certain epidemic years, the rates appear to be essentially the same. Fig. 1 illustrates the point more vividly when the cities of New York and Los Angeles are compared in graph form.

Table IV. Acute Phase Reactants in Various Disease States

CONDITION	SEDIMENTATION RATE	MUCOPROTEIN TYROSINE	ANTI-STREPTO-LYSIN TITER	C-REACTIVE PROTEIN	NONGLUCOSAMINE POLYSACCHARIDES
Acute respiratory disease	Normal or slightly increased	Normal or slightly increased	Normal	±	Normal or slightly increased
Streptococcosis	Normal or slightly increased	Normal or slightly increased	Increased	±	Normal or slightly increased
Acute rheumatic fever	Increased	Increased	Increased	+	Increased
Acute glomerulonephritis	Increased	Increased	Increased	+	Increased
Acute rheumatoid arthritis	Increased	Increased	Normal	+	Increased
Smoldering rheumatoid arthritis	Normal	Increased	Normal	±	Increased
Inactive rheumatic fever	Normal	Normal	Normal	0	Normal
Malignancy	Increased	Increased	Normal	+	Increased
Lupus erythematosus	Normal or increased	Increased	Normal	±	Increased

DISCUSSION

Although the number of patients involved in this study is small, the following impressions have been gained:

1. A small percentage (2 to 6 per cent) of the normal childhood population harbor streptococci.

2. A small percentage (3 to 18 per cent) of respiratory disease is due to streptococci, the actual percentage varying, depending upon the time of year.

3. We found it difficult to predict streptococcal infection on the basis of symptoms and physical findings alone.

4. City health department data would indicate that, except for epidemic years, the incidence of the streptococcal disease in several major large cities spread over the United States does not differ significantly. It would thus appear that differences in the *supposed* incidence of rheumatic fever in these various communities could not be accounted for on the basis of a difference in the incidence of streptococcal disease.

The incidence of streptococcal carrier state and the relative incidence of streptococci as a cause of respiratory disease found in our study compare favorably with data obtained by Rammelkamp and associates[1] in a study made on families living in Cleveland, Ohio. On an average, it would appear that the incidence is not quite as high as that found by Rantz and collaborators[6] on children seen at the Stanford Hospital in San Francisco.

Our failure to be able to diagnose streptococcal disease clinically as readily as others[5] supports the need for laboratory aid, specifically, a throat culture. Recent work[7] has demonstrated that rheumatic fever can be equally as well prevented even if the administration of penicillin is withheld for seven days following the onset of disease. This period allows the physician adequate time to make the proper studies, including a throat culture, and it also permits a moderate amount of antibody production against the specific type of streptococci causing the disease.

The problem of differentiating between uncomplicated streptococcosis and rheumatic fever can, in some instances, be very difficult. It is not the purpose of this paper to present data to support the authors' point of view as this has been done elsewhere.[8] However, the performance of a battery of tests referred to as the acute phase reactants will, in most instances, help to make the differentiation. Table IV shows the changes in the acute phase reactants in various conditions including uncomplicated streptococcosis. The normal values for these acute phase reactants are shown in Table V.

Table V. Normal Values for Acute Phase Reactants

DETERMINATION	NUMBER OF INDIVIDUALS	MEAN	MINIMUM	MAXIMUM	MEASUREMENT
Mucoprotein tyrosine	76	3.3	1.8	4.3	mg. %
Antistreptolysin-0 titer	67	55	0	333	Todd units
C-reactive protein	76	0	0	2+	mm. of precipitation
Nonglucosamine polysaccharides	75	116	85	148	mg. %
Sedimentation rate	—	7	3	11	Westergren mm. in 1 hr.

SUMMARY

1. Evidence has been presented to indicate that streptococcosis occurs with similar frequency in Southern California as in other areas throughout the United States.

2. A small percentage (2 to 6 per cent) of the normal childhood population harbor streptococci.

3. A small percentage (3 to 18 per cent) of respiratory disease in children is due to streptococci, the actual percentage depending upon the time of the year.

4. We found it difficult to predict streptococcal infection on the basis of symptoms and physical findings alone and therefore strongly recommend a throat culture as a necessary laboratory aid.

5. The acute phase reactants are valuable laboratory aids in differentiating uncomplicated from complicated streptococcosis.

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September 14, 1772. Went after dinner to Corotoman, where Mr Carter and his Lady, who came to my house on the Saturday before I got off, had got home before me; and, poor Lady, she just saw her little and only boy smile and dye. A very shocking sight indeed! But is it not wrong, for parents to leave such an infant, altho' to careful people, yet not to those who feel as parents. I understood this Child had been taken ill about a fortnight before with a purging, but a little Rhubarb had stopped it, till convulsions obliged the sending for a Dr, and he a young man, and perhaps unacquainted with disorders peculiar to children; when perhaps a little Ipecac tea, a clyster to divert and remove the complaint from the brain, or a blyster would have saved the child.

DIARY OF COL. LANDON CARTER. WILLIAM & MARY QUARTERLY, XIII (1905) 159.

MIGRATION OF SPIKE FOCI FROM ONE HEMISPHERE TO THE OTHER IN CHILDREN

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A SPIKE focus in the electroencephalogram usually remains in the same place for several years. It may, however, migrate to the other hemisphere as will be shown in the following report of five cases.

During the last five years 5,000 patients suffering from epilepsy have been registered at the electroencephalographic laboratory of the Department of Neurology, Rikshospitalet. In five patients a new and apparently independent spike focus appeared in the other hemisphere.

The electroencephalograms were registered with an eight-channel Kayser electroencephalograph. Bipolar as well as monopolar recording was used. Some of the patients were registered during sleep. In some cases flicker stimulation was employed.

CASE REPORTS

CASE 1.—L. S., born Aug. 19, 1946. The family history was normal. Etiology was unknown. The first seizures occurred about the age of 5 years, starting in the right arm. The patient became unconscious and there was a postparoxysmal sleep. From the age of 6 or 7 years the seizures changed pattern and started in the left arm before turning into general jerks.

Treatment consisted of phenobarbital plus diphenylhydantoin until symptoms of intoxication developed without effect.

EEG 1 registered Nov. 13, 1951, at the age of 5 years 3 months: normal. EEG 2 registered Oct. 2, 1952, at the age of 6 years 2 months: Spikes in left parietal region. EEG 3 registered Oct. 20, 1953, at the age of 7 years 2 months: Sharp waves plus theta delta activity in left parietal region. EEG 4 registered May 5, 1954, at the age of 7 years 9 months: Bilateral theta activity. EEG 5 registered Sept. 27, 1954, at the age of 8 years 1 month: Spikes in left as well as right parietal region. EEG 6 registered March 21, 1955, at the age of 8 years 7 months: Spikes only in right parietal region.

CASE 2.—A. P., born Nov. 21, 1944. The mother had an untreated syphilitic infection. The patient was delivered by forceps. The patient had congenital syphilis treated with Spirocid tablets in the neonatal period. At the age of 3 years she had a serious head trauma with hematoma on the left side. The first seizure appeared at the age of 6 years, starting in left half of the face, spreading to left half of the body before the convulsive movements became general.

The patient was seizure-free on 0.10 diphenylhydantoin plus 0.05 Gm. phenobarbital. At the age of 7 the same seizures appeared after a few days' cessation of the antiepileptic treatment. Since then she has been given the same doses and has remained free from seizures.

Pneumoencephalogram was normal at the age of 6 years. Blood Wassermann test was positive (++) at the age of 7, negative at the age of 8 years.

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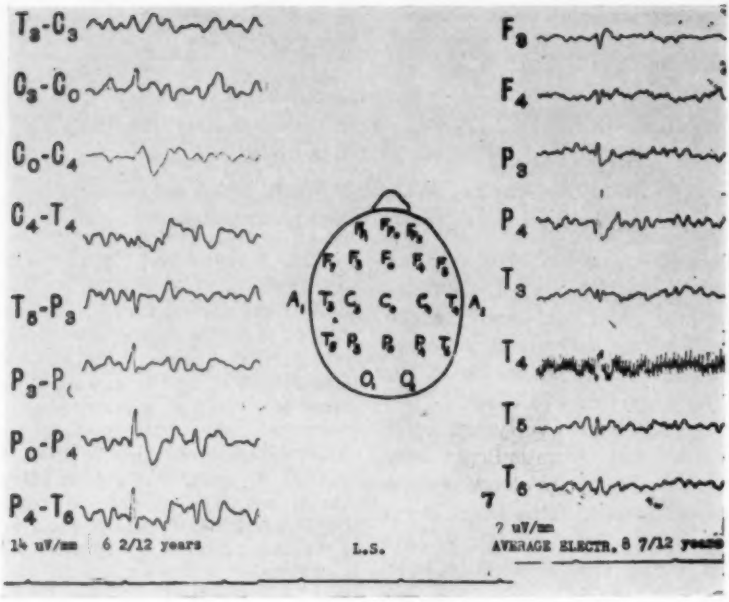

Fig. 1.—Migration of spike focus from the left to the right parietal region. Case 1.

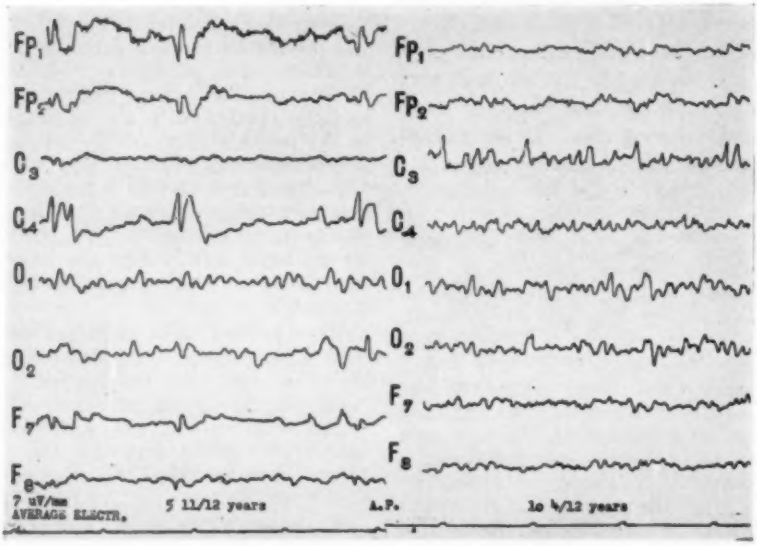

Fig. 2.—Migration of spike focus from the right to the left central region. Case 2.

EEG 1 registered Oct. 31, 1950, at the age of 5 years 11 months: Spikes and reduction of the cerebral activity in right central region. EEG 2 registered Jan. 9, 1952, at the age of 7 years 2 months: Spikes and reduction of the cerebral activity in right central region as well as some bilateral spikes. EEG 3 registered Jan. 7, 1953, at the age of 8 years 2 months: Spikes in right central region. EEG 4 registered March 3, 1954, at the age of 9 years 3 months: Sharp wave in right central region plus left temporal region. EEG 5 registered March 17, 1955, at the age of 10 years 4 months: Spikes in left central region. EEG 6 registered May 16, 1955, at the age of 10½ years: Sharp waves in left frontal region.

CASE 3.—P. E. B., born Dec. 30, 1948. The family history was normal; mother primipara; forceps delivery, weight at birth, 4,500 grams. The first attack appeared as a right-sided paroxysmal headache, followed by sleep at the age of 4½ years. At that time the patient had mumps, but no clinical symptoms of encephalitis.

The patient's attacks of headache stopped after he was given two doses of 0.05 Gm. diphenylhydantoin a day.

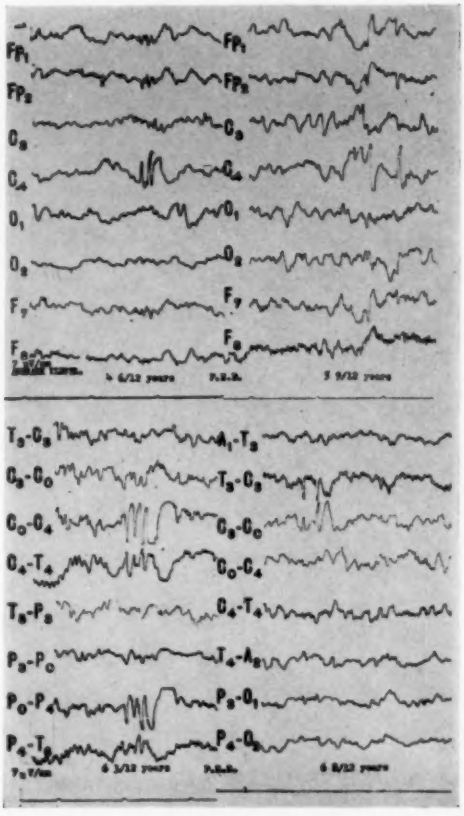

Fig. 3.—Migration of spike focus from the right to the left central region. Case 3.

X-ray of cranium: Negative (at the age of 4½ years).

EEG 1 registered June 1, 1953: Spikes and reduction of the cerebral activity in right central region. (Sleep —EEG.) EEG 2 registered Aug. 21, 1953, at the age of 4 years 8 months: Spikes and reduction of the cerebral activity in right central region. EEG 3 registered Feb. 12, 1954, at the age of 5 years 2 months: Spikes and reduction of the cerebral activity in right central region, most prominent during sleep. EEG 4 registered March 25, 1955, at the age of 6 years 3 months: Spikes in left central region.

CASE 4.—F. J., born Jan. 23, 1946. Mother suffered from epilepsy. Etiology was unknown. The first seizure was at the age of 6 years, starting with jerks of the right side of the mouth, and dysphasia.

The patient was seizure-free on 0.05 Gm. phenobarbital for two years. After a discontinuation of medication for two days, at the age of 8 years, the patient's seizures reappeared; however, after continuation of treatment, he has been seizure-free again.

EEG 1 registered June 1, 1953, at the age of 7 years 4 months: Spikes in the right central region. EEG 2 regis-

Fig. 4.—Migration of spike focus from the right to the left central region. Case 4.

tered Dec. 16, 1953, at the age of 7 years 11 months: Spikes in right central region. EEG 3 registered June 23, 1954, at the age of 8 years 5 months: Spikes in right and left central region plus spike waves bilateral synchronously. EEG 4 registered Dec. 1, 1954, at the age of 8 years 10 months: Spikes practically only in left central region.

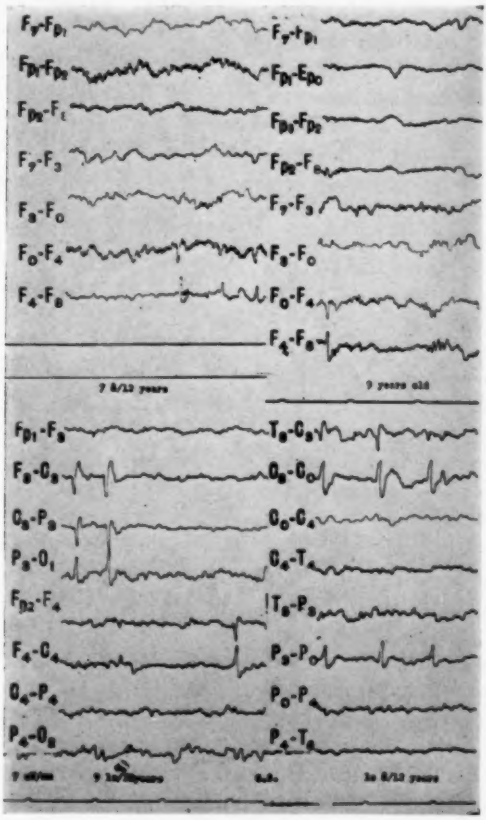

Fig. 5.—Migration of spike focus from the right frontal to the left central region. Case 5.

EEG 5 registered Jan. 26, 1955, at the age of 9 years: Spikes only in left central region.

Case 5.—G. S., born June 26, 1944. The family history was normal. Etiology was unknown. First seizure appeared at 6½ years of age. The seizures started with the patient complaining of a queer feeling in the mouth; jerks in the arms and legs appeared, and he lost consciousness. Postparoxysmal sleep. The patient was free from seizures on 0.10 Gm. diphenylhydantoin.

EEG 1 registered Feb. 4, 1952, at the age of 7 years 8 months: Spikes in right frontal region. EEG 2 registered June 9, 1953, at the age of 9 years: Spikes in right frontal region. EEG 3 registered April 13, 1954, at the age of 9 years 10 months: Spikes in right frontal region plus left central region. EEG 4 registered Feb. 9,

1955, at the age of 10 years 8 months: Spikes only in left central region.

DISCUSSION AND CONCLUSION

Migration of spike foci from one hemisphere to the other has been known for several years. In typical cases they appear as mirror foci. The spikes here have lower voltage and longer duration and appear from 5 to 15 m.s. later than the original spikes.[1] The spikes appearing in a so-called mirror focus may, however, have a higher voltage as well as shorter duration than the original spikes. They can also apparently appear independent of these. On rare occasions the primary focus may disappear completely, while the secondary remains. It is thus difficult to decide if a mirror focus really is secondary to the primary or if both foci maybe are secondary to another process, possibly situated subcortically. A third possibility is that the mirror focus as well as the original focus are both primary cortical lesions which have become epileptogenic at different times.

Supporting the first theory, that a mirror focus actually is secondary to the primary focus, a series of convincing experiments have been performed, among others, by Jasper and associates[1]: by applying alumina cream focally to the cortex in monkeys they found in the EEG, first, suppression in the treated area. Later a focal slow activity appeared, which little by little became epileptogenic. At that stage the monkeys began to have focal epileptic seizures corresponding to the site of the lesion. Three to four months later a mirror focus was registered in the other hemisphere. Sharp waves and spikes in this mirror focus appeared, partly independent of the contralateral spikes. The mirror focus did not change if intersection of corpus callosum or surgical removal of the original lesion was performed. From these experiments, Jasper and co-workers suggest that a prolonged bombardment from a primary focus may cause another epileptogenic lesion.

Gibbs and associates[2] described another type of migration in children. They found that occipital spike foci in infants moved forward with increasing age. The clinical seizures changed type according to the area where the spike foci moved, but in children with cerebral palsy, the neurological symptoms remained unchanged (20 per cent of his forty-five cases had cerebral palsy).

In Cases 1, 2, and 3 there were focal epileptic seizures corresponding to the spike focus in the EEG. In two cases, patients 2 and 3, a reduction of the electrical cerebral activity in the same area was also registered. Case 1 had a focal theta delta activity in the same area. The electroencephalographic findings compared with the focal epileptic seizures of these three patients strongly indicate that all of them have relatively limited cortical epileptogenic lesions.

Before the spike focus migrated to the other hemisphere, the epileptic seizures ceased in two patients. In spite of the antiepileptic treatment patient 1 continued to have seizures, but they changed character. Instead of starting in the right arm, as they did in the beginning when spikes were registered from the left parietal region, these latter attacks started in the left arm. A corresponding change

was found in the EEG as the spike activity now only occurred in the right parietal region (Fig. 1). This should indicate that it was the epileptogenic lesion itself which had migrated from one hemisphere to the other. Should this be the case, the explanation of the migration might be that bombardment of a primary focus has produced a secondary epileptogenic lesion.

demonstrated in the EEG of Case 4 may suggest an affection of a deep medial structure (Fig. 6.) A marked discrepancy between the focal epileptic seizures and the first spike foci in the EEG was also found, and this is rare in cortical epileptic lesions.

In Case 5 the migration of the spike focus occurred from the right frontal region to the left central region. This is unusual, but the possibility that the

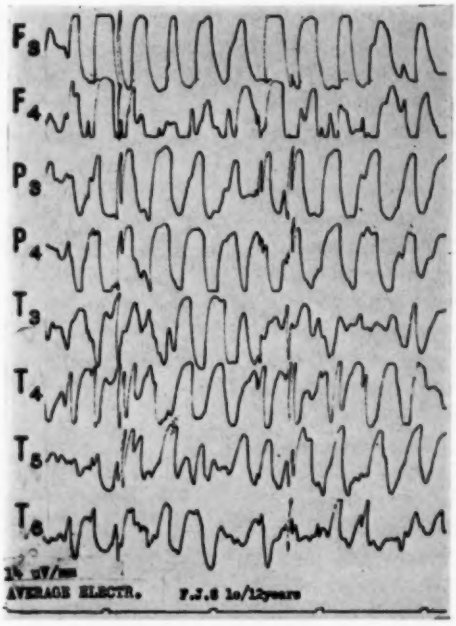

Fig. 6.—Bilateral spike and waves. Case 4.

In the last two cases the electroencephalographic changes may also be explained by the same theory. In these two cases, however, and especially in Case 4, the second theory, the so-called primary focus as well as the mirror focus are secondary to a third lesion situated subcortically. The bilateral synchronous spike and waves

primary focus is situated subcortically cannot be excluded.

Both the electroencephalograms as well as the focal epileptic seizures in the first three patients are strongly indicative of primary cortical epileptogenic lesions, but bilateral spikes in the EEG were registered in Case 2. Focal epileptic seizures as well as

an apparent cortical spike focus may, however, originate in the depth.[1] Even if a subcortical lesion in the three latter cases is less probable, the possibility cannot be excluded.

The third theory of several cortical lesions becoming epileptogenic at different times may be the explanation in Case 1. There is a possibility of a parasagittal lesion which at first was epileptogenic on the left side, then on the right side. The same possibility cannot be excluded in the other patients. Particularly on account of the possible etiological factors—syphilis and possible encephalitis—in Cases 3 and 4, the existence of several cerebral foci is possible.

The patients reported above constitute a very heterogenous group regarding etiology, type of seizures, as well as electroencephalographic findings. The only thing common to all of them is the age group in which the migration occurred.

Our findings are in accordance with Gibbs and Gibbs. Their comments are: "The general sense of the evidence indicates that the discharging lesion and the structural lesion are distinct and independent. Unlike the structural lesion, the discharging lesion can migrate, and it commonly heals completely. Healing on the discharging lesion appears to depend on some as yet unknown processes that are intimately related with growth and development."

The migration of spike foci from one hemisphere to the other in these patients may thus be explained by all the theories here mentioned. Gibbs and Gibbs' theories are perhaps the most probable as the only common factor in our patients is that they are all children.

SUMMARY

In five children an electroencephalographic spike focus migrated from one hemisphere to the other after having remained constant for two to four years. The original spike focus disappeared completely. The possible theoretical causes are discussed. The migration and the healing of the discharging lesion may depend on some processes related with growth and development.

We wish to express our appreciation to the heads of the departments, Professors S. Refsum, M.D., and L. Salomonsen, M.D.

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THE OPERATIVE TREATMENT OF PECTUS EXCAVATUM

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A CONSIDERABLE number of deformities of the chest wall challenge the skill and the ingenuity of the surgeon. The sternum may be entirely bifid with or without ventral displacement of the heart. This is a serious anomaly, relatively readily repaired early in infancy, and only with difficulty or not at all, subsequently. We have had the opportunity to treat a number of children with absence of ribs in various portions of the thoracic cage. These have been repaired by varying combinations of osteoplastic procedures on the ribs and fascial grafts or reinforcements. Pigeon breast (pectus carinatum) with its forward thrust of the sternum and deep lateral depressions on either side is another striking deformity which has yielded gratifyingly to surgical correction. However, the largest experience to date with repair of the deformities of the bony thorax has to do with the condition known as pectus excavatum or funnel chest, called by earlier writers Trichterbrust.

Pectus excavatum is a congenital anomaly in which the body of the sternum is depressed to form a concavity which may reach to the vertebral bodies, or, passing to one side, into the paravertebral gutter. The lower costal cartilages on either side bend back toward the dorsally displaced sternum, giving breadth to the concavity, the depth of which is usually maximal just above the xiphisternal junction. There is, therefore, a concavity from side to side and from above downward. The deformity is commonly noted soon after birth and the feature of greatest importance is the tendency toward progression. The degree and rate of progression are variable and inconstant. In most of our patients the deformity has been noted at birth, but, in a few, competent observers failed to observe the deformity until the infant was several weeks or months old. The concavity is conspicuous and unsightly and a source of embarrassment to young individuals of either sex. The deformity of the rib cage and the spine in the more severe instances is quite plain, even when the patient is clothed. These patients usually have a thorax with decreased anteroposterior diameter, a moderate dorsal kyphos, and carry their heads thrust forward. Paradoxical inward motion of the sternum with inspiratory movement is a conspicuous feature of the deformity in infants and children, until, with increasing years, the chest wall becomes rigid. This paradoxical inspiratory motion of the sternum may be seen to an astonishing degree in infants with the deformity. There is commonly a prominent protrusion of the abdomen on

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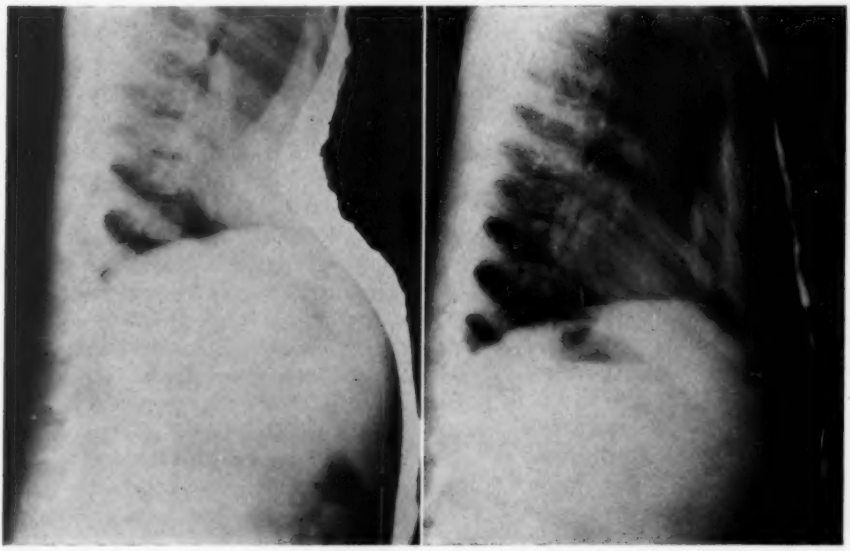
inspiration. The etiology of the deformity is not well established. It is commonly ascribed to a shortening or contracture of the central tendon of the diaphragm. That the deformity is increased by the pull of the diaphragm, is beyond question, but it may be observed that the maximal depth of the deformity is frequently some distance above the level of the of the costal cartilages may be primary rather than secondary.

In some instances, the heart is compressed between the spine and the sternum, but, more often, the depression of the sternum displaces the heart to the left even in the less severe cases. In the more severe deformities, the heart is displaced far to the left and rotated posteriorly.



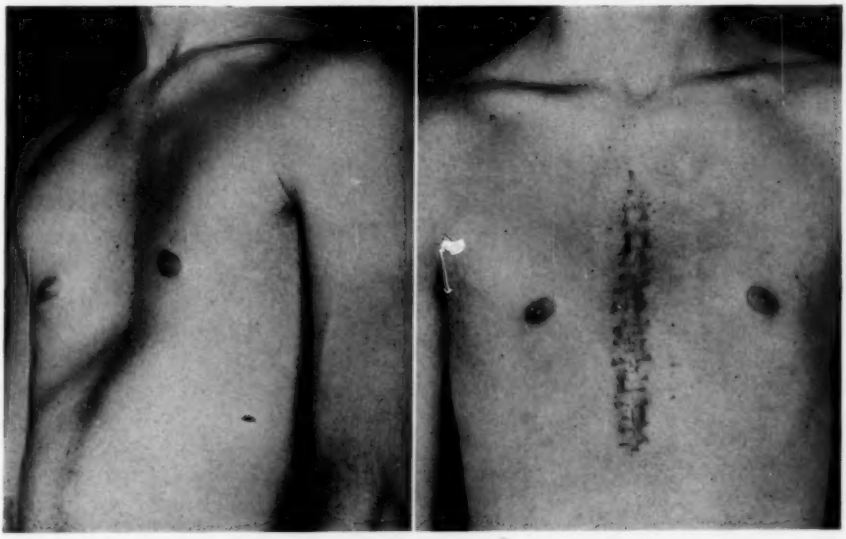
A. *B.*

Fig. 1.—P. S., 3 years of age. *A*, Preoperative roentgenogram, showing marked dorsal displacement of the sternum, which nearly touches the vertebral bodies. *B*, Postoperative roentgenogram, showing great increase of space between spine and sternum, into which the heart has moved.

diaphragmatic attachment. Furthermore, the appearance of the deformity at birth in these patients would leave one to assume that some mechanism other than diaphragmatic pull was responsible. Rickets and scurvy are certainly not involved. The costal cartilages are obviously increased in length in following an indirect course to the sternal border, and it has been suggested that the increase in length

Pushed out in the left hemithorax, in a patient with a flat, thin chest, the heart gives the impression of being imprisoned in the flattened chest between the anterior and posterior parietes—and, in fact, it may be so imprisoned. Such a degree of deformity does not often develop before adolescence, but it is not possible to predict which infant with pectus excavatum will go on to develop a severe deformity and which will not.

The physiological consequences of this deformity appear to have been neglected. While severe cardiac embarrassment is rare, it does occur. We have operated upon one patient[1] who had had two attacks of cardiac failure and presented in one of these attacks with auricular fibrillation. After initial treatment with digitalis and quinidine, his thoracic deformity was corrected. He returned to full activity as an interurban bus driver, and has been well for over five years. He has a regular rhythm and takes no medication. Another patient had been treated for a year because of a diagnosis of hyperthyroidism based on a persistent tachycardia, which receded after correction of her deep funnel chest. There are several reports of patients who have died with dyspnea and cardiac failure, in whom at autopsy no abnormality could be found except a severe pectus excavatum. However, this degree of cardiac embarrassment is uncommon. Infants and small children are usually totally asymptomatic so far as their hearts are concerned. However, we are frequently told by their parents that after operation the children are more energetic and vigorous than they had ever been before. Older children and young adults will practically all have some demonstrable degree of limitation of exercise tolerance. It may be no more than that of the college student who could play one set of tennis but not two, or of the high school boy who could race one lap around the track but no more, or of the Boy Scout who could go on hikes with his comrades, but invariably fell behind when the going was uphill. These symptomatic findings can be correlated to some degree with



A. *B.*

Fig. 2.—C. B., 21 years of age. *A* and *B*, Preoperative and postoperative photographs, showing the degree of deformity which produced mild but definite limitation of capacity for exercise in this young college student, relieved entirely by operation.

clinical investigation. Studies with the electrocardiogram with multiple precordial leads and, more recently, particularly, with the vectorcardiogram, show evidences of cardiac irritability, arrhythmias, and varying degrees, often quite marked, of rotation. These findings are usually reversed by operation. A good many of these patients have been noted to have systolic "functional" murmurs which may or may not disappear after operation. An unexpected finding in the infants operated upon for pectus excavatum was the report by the mothers that the infants fed better than before. In only one or two infants have we had before operation a definite story of an unusual degree of regurgitation or of difficulty in swallowing, but in a good many infants we have been told after operation that the child swallowed with such ease, that the mother was aware for the first time that there must have been some difficulty in swallowing before operation. In many children, before operation, there is a history of repeated respiratory infections.

The older children are frequently conscious of their deformities, and, especially in the case of boys, suffer a good deal of teasing from their playmates. It is in these older children, too, that there often occurs after operative correction the sudden discovery of increased exercise tolerance, although it had not been appreciated before that any limitation of exercise tolerance existed.

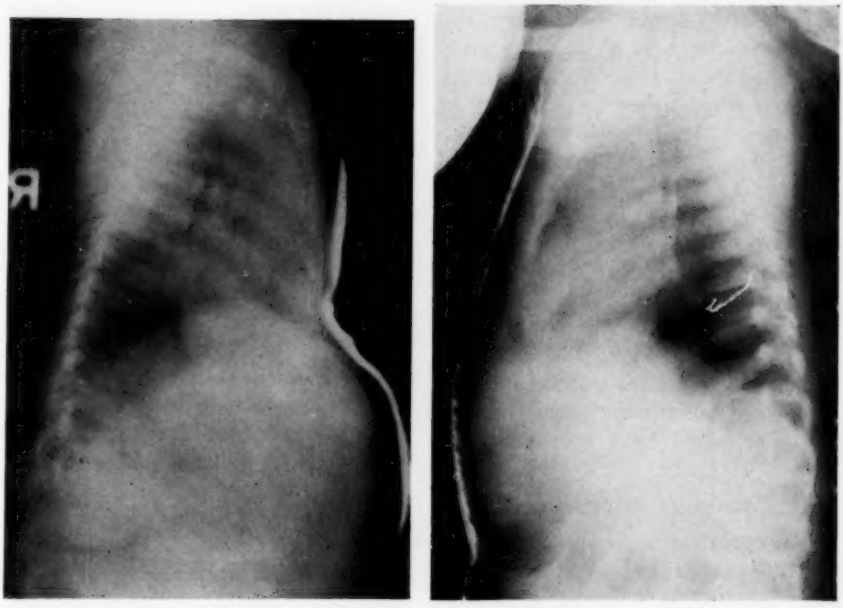
INDICATIONS FOR OPERATION

It is to be emphasized that infants and small children have few, if any, symptoms even when the deformity is severe. However, it is our feeling that operation should be undertaken in all fairly marked instances of pectus excavatum in infancy and childhood, in the absence of other and overriding defects or disabilities, such as cardiac anomalies or multiple skeletal anomalies of the type seen in Marfan's disease. Funnel chest is seen with considerable frequency among children with congenital cardiac defects or multiple skeletal defects. Daniel[2] has recently operated upon several children with pectus excavatum and cerebral spastic disorders because of repeated respiratory infections, with encouraging results.

Operation is undertaken to correct the existing deformity and to prevent its progress. The younger the patient at the time of correction, the more favorable are his chances of attaining a normal thoracic contour with subsequent growth of the rib cage. If the deformity is severe, or if a competent pediatrician has observed it to progress, operation is undertaken at any age. Our youngest patient was 3 months old at the time of operation.

Operation is therefore undertaken for physiologic, orthopedic, and cosmetic reasons. If dyspnea, exercise intolerance, or cardiac arrhythmias are present, operation is strongly indicated. However, most children have no such symptoms and operation is generally advised even in their absence. In children with pronounced defects, operation should be undertaken before there is any evidence of physiologic disturbances. One cannot predict which children will ultimately suffer most if not operated upon. On the other hand, one may say that a less formidable procedure in infancy will probably ensure normal development, whereas more extensive operation some

A. *B.*



C. *D.*

Fig. 3.—Infant, 12 months of age. *A*, Photograph before operation, showing fairly pronounced defect, with child at rest. Deep inspiration caused striking paradoxical inward motion of sternum. *B*, Two months after operation the thoracic contour is seen to be quite normal. Infants tolerate the operation well. No external traction is employed and hospitalization is usually brief. *C* and *D*, Roentgenograms before and two months after operation. Note the increased fullness of the chest and the increased distance between the heart and the vertebral column.

years later may produce only a partial correction of the deformity. We do, of course, see a good many children with trifling sternal depressions whom we dismiss as not requiring operation.

The anteroposterior flattening of the chest and the kyphosis may improve or disappear if operation is performed early enough. The younger the patient is, the simpler and smaller the procedure and the better the results that may be expected. Corrective exercises cannot be expected to achieve much for an actual skeletal deformity such as this.

The deformity itself is the source of concern to children and parents and the basis for teasing by playmates. A sunken chest, with the clothes worn by both sexes today, can scarcely be hidden, particularly in the summertime. The extent to which a patient and his family have been disturbed has usually been fully appreciated only after the operation. Parents are apparently loathe to admit to wanting an operation of this character for what they construe to be cosmetic reasons, but the correction of the defect seems to permit the patient and family alike to discuss freely what had previously been minimized by a protective reticence.

TECHNIQUE OF OPERATION

The operation as performed at present differs in a few details from that reported in 1949.[3] We aim to prevent progression of the deformity and to correct the deformity already existing. The operation is designed to remove the distorted cartilages, to fix the sternum solidly in its proper position, and to free it from all structures which might tend to maintain or recreate the deformity. Under intratracheal anesthesia, a midline incision is made from manubrium to epigastrium, down to the sternal periosteum and the linea alba. Pectoral muscles are stripped back in a sheet on either side without any preliminary elevation of skin flaps. With proper instruments, even in the smallest infants, subperichondrial resection of the cartilages can be readily effected and we find that with the perichondrium left behind, the chest wall becomes firm much sooner, usually within three weeks. As many cartilages as are deformed are removed for the full length of their involved segments, usually four or five, often out to the costochondral junction and occasionally beyond. The xiphisternal joint is divided. We are seldom able to find any structure of significance to call a substernal ligament. The intercostal bundles are divided from the sternum, isolating the sternum entirely as a peninsula, attached only above to the manubrium. A transverse cuneiform osteotomy is performed at the cephalad limit of the sternal deformity cutting through only the anterior cortical lamella, and curetting out a little of the cancellous bone. The sternum is lifted forward, and bent back and forth until the posterior cortical lamella, its only attachment, is fractured, correcting the posterior displacement. In older children and in young adults, we usually cut a half centimeter slice out of the costal cartilage above the highest one resected. This permits us to perform the sternal osteotomy one interspace higher, thus achieving maximal correction. At the same time, it permits fixation of the sternum not only across the sternal osteotomy, but also across the two cartilage incisions. The sternum is maintained in the corrected

position by mattress sutures of heavy silk placed across the osteotomy. We feel that silk is less likely to break than wire, and much less likely to cut through the bone. In addition, the sternal periosteum is carefully repaired with interrupted sutures of silk. In those patients in whom one more costal cartilage has been transected, a heavy silk suture is used to unite the cartilages. The intercostal bundles are occasionally tacked lightly to the undersurface of the sternum, if this does not appear to exert any traction upon the sternum. The xiphoid is left detached. The pectoral muscles are tacked back to the sternum in the midline. No external traction[4] or fixation of any kind is employed, and we have not found any to be necessary, nor have we seen need for struts of rib for support.[5] We do not perform the "limited" operation of Brown[6] on any patients, and in one patient have operated after such a procedure had been performed with what parents and pediatrician thought was no change.

POSTOPERATIVE CARE

Postoperative respiratory distress is uncommon. Most of the patients do not require oxygen and significant paradoxical respiration does not occur. One can always see an area of paradoxical motion which is actually in the epigastrium and involves the area between the detached xiphoid and the sternum. This motion disappears within two to three weeks. Some authors mention the need for tracheotomy in infants after this operation. Its use has not had to be considered. The patients may have tachycardia and fever for a day or two, but they are up and about on the second or third day. Fluid frequently collects between the skin flaps and requires a needle aspiration until it fails to re-form. If it is not aspirated with sufficient promptness, it may force its way out through the wound. No protective dressing or apparatus is employed and for the past year we have been dressing these wounds solely with an aerosol spray of translucent rubber cement-like material. The patients usually leave the hospital five to seven days after operation.

RESULTS

Our experience now comprises fifty operations for pectus excavatum performed on forty-three children and seven adults varying in age from 3 months to 38 years. The operation is no more difficult in the infants than in the older children and is certainly much easier in both than in adults. The babies tolerate the procedure very well and it has therefore been our practice to ignore the factor of age, making the decision to operate in infants and children whenever operation appears required for a deep or progressing deformity. There has been a single death, previously reported, in the second child operated upon, who developed a massive and immediate wound infection. There has been no other serious complication. Entrance into the pleura is not a rare occurrence, but is of little moment. The results have been satisfactory and sustained, both as regard the sternum and thoracic contour and as regard the general condition of the children. While the anterior portion of the thorax may often appear rather flat after operation, as opposed to the rounded chest of a normal child, it is never sunken. In two children, one a

boy of 3 years, one a boy of 14 years, the depression is gone, the general result is good, and the adolescent notices considerable improvement in exercise tolerance, but the sternum is not solidly united and tends to slope downward and in. In both these instances, it was proposed to place a strut beneath the lower end of the sternum, such as is recommended by several authors. However, in both instances the parents have stated that they are far too well satisfied with the result to be interested in another operative procedure. It is regularly reported by the parents that the children eat better and play more vigorously. The adolescents and young adults remark upon increased exercise tolerance and freedom from fatigue, even when they had made no complaints in these respects before operation. Those patients with cardiac difficulties before operation have been relieved of these, and in most instances the electrocardiographic and vectorcardiographic evidences of cardiac displacement and rotation have disappeared.

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Whereas by long experienc itt is found very Unsutable & inconveyent for swine to goe att libertye in the towne, and Exceeding hazerdous for the lives & limbes of young children to have them goe up & downe in the streetes & lanes thereof

Wee doe therefore order that there shall not any swine bee suffered to goe in any streets or lanes of the towne from the bridge to the poynt of Rocks.

—SALEM, MASSACHUSETTS, TOWN RECORDS, 1680.

THE PROTECTIVE EFFECT OF GLYCINE AGAINST THE INHIBITION OF UREASE BY A QUATERNARY GERMICIDE

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STUDIES concerning the effect of quaternary germicides on the urease activity of *Proteus mirabilis*, made because of the use of these agents as deterrents for "ammonia dermatitis," have shown that the development of the urease activity is delayed or inhibited when this organism and certain others are exposed to fabric impregnated with various concentrations of several quarternaries.[1, 2] Quaternary germicides incorporated in ointments, tales, starches, etc., are recommended for dermal irritations due allegedly to ammonia arising from the microbial decomposition of urinary urea or from the action of free urease, undigested in passage through the gastrointestinal tract or elaborated by intestinal microorganisms.[3-6]

In order to investigate the relationship of quaternary germicides to the enzyme, cells of *P. mirabilis* were disrupted with 2 M glycine to release bacterial urease. The ureolytic property of the juices so obtained was of an exceedingly low order but suggested that the effect of quaternary germicide on vegetable urease might yield information applicable to the problems relating to the use of quaternary salts to prevent urease activity of microbial or vegetable origin.

A comparison of the activity of jack-bean urease in 2 M glycine and phosphate buffer and the inhibitive effect of a quaternary in these diluents gave results which seemed of some value to those employing urease for diagnostic purposes and quaternaries for their bacteriostatic or bactericidal properties. These results are presented.

From the Agricultural Research Service, U. S. Department of Agriculture.

MATERIALS AND METHODS

Two milliliters of purified Arlco jack-bean urease in phosphate buffer (9.1 Gm. KH_2PO_4 and 9.5 Gm. Na_2HPO_4 per liter) and in 2 M glycine at pH 7 were combined with 0.1 ml. of the quaternary salt, alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride and kept at 45° C. for fifteen minutes. Digestion for thirty minutes followed the addition of 0.5 ml. of 4 per cent urea in phosphate buffer before the reaction was stopped with 1.0 ml. of 1 N HCl.

To determine the activity of the enzyme, 0.1 ml. water replaced the quaternary in the reaction mixture. The ammonia formed was calculated as milligrams of nitrogen.[7, 8]

RESULTS

Fig. 1 shows that the activity of jack-bean urease in glycine consistently exceeded its activity in phosphate, and in low concentrations it was as much as six times as great. With 2 to 3 mg. of enzyme the activity in phosphate approaches that obtained in

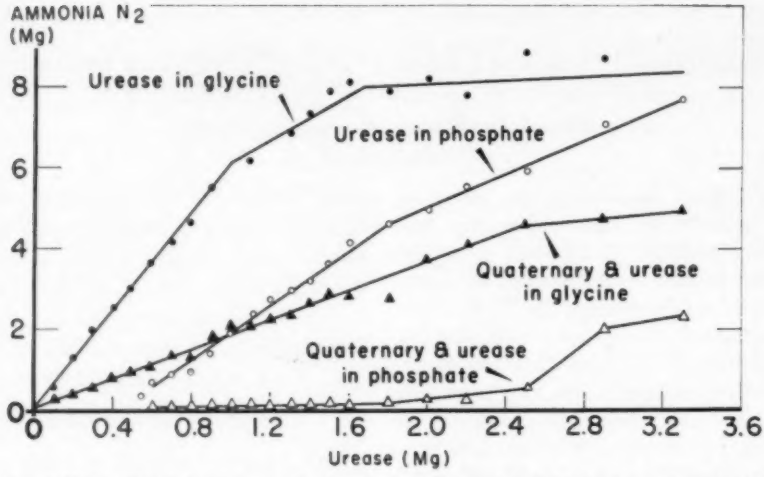

Fig. 1.—Activity of jack-bean urease in phosphate buffer and in 2 M glycine and the inhibition induced by 4 mg. of quaternary germicide.

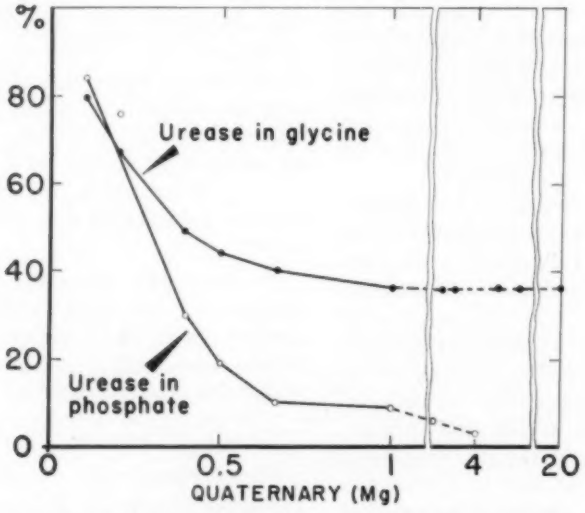

Fig. 2.—Effect of increasing concentrations of quaternary germicide on 1.3 mg. jack-bean urease in phosphate buffer and in 2 M glycine.

glycine with 1 to 2 mg. It should be noted that the ratio of the ammonia produced to concentrations of urease in the respective diluents gives a characteristic constant up to 1 mg. in glycine and 1.8 mg. in phosphate buffer.

Observation of the curve depicting the effect of quaternary on enzyme in phosphate shows that 4 mg. of the germicide almost completely inhibited 2 mg. of urease in phosphate, but in a reaction mixture containing 3.2 mg. urease, as much as 30 per cent of the activity was obtained when 4 mg. quaternary was present. These results are not unexpected since large organic cations inhibit certain enzymes.[9] This observation is also in accordance with unpublished results obtained in this laboratory which showed a proteolytic enzyme from a Streptomyces was partially inhibited by 1:1,000 dilution of this same quaternary.

In glycine the effect of the quaternary on the urease was marked by a linear relationship up to 2.5 mg. of the enzyme. The loss of activity due to the quaternary was approximately 65 per cent in the portion of the curve in which the ammonia nitrogen produced was proportional to the concentration of the enzyme.

Fig. 2 shows the effect of increasing the concentrations of quaternary on 1.3 mg. of urease in phosphate and in glycine. In phosphate about 84 per cent of the enzyme activity was obtained with 0.1 mg. of quaternary, but a sharp drop occurred when 0.4 mg. was used. That these concentrations delay the urease activity of *P. mirabilis* has been noted; the prevention of ammonia formation from urea was the criterion for bacteriostasis. The enzyme activity decreased to 3 per cent on the addition of 4 mg. of quaternary, a concentration which falls within the range found bactericidal for *P. mirabilis*. It should be mentioned at this point that the unreliability of certain urease preparations might be due to quaternary germicide adherent to glassware in laboratories where these agents are commonly used for disinfectants.

In glycine, 0.1 mg. of the quaternary permitted about 80 per cent of the activity of the enzyme, whereas 1.0 mg. allowed 35 per cent. Increasing the quaternary to 20 mg., fifteen times the concentration of the enzyme, induced no further change in the production of ammonia nitrogen. Thus, as much as 35 per cent of the activity of the enzyme was retained when concentrations of either enzyme or quaternary were varied.

The enhanced activity of urease in glycine suggests the use of glycine solutions to aid in detecting this enzyme in tissues not otherwise apparent. It is interesting to speculate also on the function of glycine or other amino acids in the urease activity of living cells. If bacterial and vegetable urease are identical, the conclusion might be made that the bacteriostatic action of this quaternary on Proteus may be attributed at least in part to the interference of the enzyme urease.

Furthermore, results of these studies might indicate that quaternary germicides could be used to repress the activity of free urease, but the success would be modified by the possibility of partial protection by such agents as glycine, if present.

SUMMARY

1. The activity of jack-bean urease in solutions of 2 M glycine has been shown to be considerably greater than

the activity of the urease in phosphate buffer.

2. The quaternary, alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride markedly inhibited the activity of urease in phosphate, from 100 to 30 per cent, depending on the concentrations of the enzyme and quaternary.

3. In glycine the enzyme was partly protected from the inhibitive effects of the germicide; with 0.4 to 1.8 mg. enzyme and 4 mg. quaternary, approximately 35 per cent activity was obtained.

4. With increasing concentrations of quaternary (0.1 to 20 mg.) and a constant amount of urease, the enzyme activity in phosphate was reduced to zero, whereas in glycine approximately 35 per cent activity was retained, even when the concentration of quaternary was fifteen times that of the enzyme.

5. The successful use of quaternary germicides in ointments, tales, starches, etc., to inhibit the activity of free urease might depend on the enzyme-inhibiting or protective substances present.

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EPIPHORA IN INFANTS

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EPIPHORA is the imperfect drainage of tears through the lacrimal passages so that tears fall over the lid margin onto the cheek. It is not hereditary or familial. This condition must be differentiated from excessive lacrimation which is the overproduction of tears. The etiology and therapeutic procedures in infants differ from those in older children and adults. The early recognition of this common condition and its prompt treatment will avoid many complications. Experience shows that many general physicians and pediatricians are not aware of the current concepts in the treatment of epiphora. A review of the nonophthalmologic medical literature fails to reveal the presence of this information. It is for this purpose that this article is presented.

ETIOLOGY

The etiology of epiphora is the direct result of one or more of the following conditions:

1. Embryological variations: misplaced or abnormal puncta so that tears cannot enter, or passages blocked by atresia and/or congenital membranes.
2. Trauma or foreign bodies in the lacrimal passages.
3. Pathologic conditions of the nasal structures affecting the lacrimal drainage apparatus.
4. Inflammation of the lacrimal system.
5. Patent, but functionally inefficient, lacrimal drainage mechanism.

When an infant is observed to be suffering from epiphora the etiology must be accurately determined. Successful therapy depends upon the prompt and adequate treatment of the underlying cause.

THE PUNCTA

Occasionally one or more of the puncta may be absent. This results from an embryonic failure in the dehiscence of the overlying conjunctival epithelium which persists as a fine membrane. This anomaly is usually seen involving only the lower puncta which may be completely absent, but more often is evident only as a slight dimple. The treatment involves the establishment and maintenance of an orifice to the canaliculus by the use of a sharp wire probe and further dilatation of this opening. The lower punctum is responsible for drainage of approximately 70 per cent of the lacrimal fluid.

Although various anomalies in the position of the puncta have been described, only congenital eversion is common enough to be considered at this time. If a punctum is not in contact with the lacrimal fluid, it will not function in efficient drainage of tears. The most common misdirection is up and/or outward on the lid margin. Normally the punctum should not be visible as the eye looks upward. The malposition of the punctum may be congenital, or secondary to lid edema, conjunctivitis, blepharitis, or derma-

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titis. Treatment of this condition is directed toward removing any obvious etiology. If the malposition of the punctum is congenital, it should be immediately corrected by surgery. The procedure varies from the simple application of electrocautery to the more extensive techniques requiring an inlay graft.

Stenosis of the punctum may be the result of congenital variations, inflammation, or trauma involving the lid margin, which results in cicatrization. Immediate attempts should be made to enlarge the orifice of the punctum with a dilator, a procedure which may have to be repeated several times. Should this fail, the posterior wall of the punctum may be excised to create a permanently enlarged orifice. It should be emphasized at this time that slitting of any portion of the canaliculus is contraindicated and only leads to serious complications. To maintain the patency, a polyethylene tube may be required temporarily. Should the above procedures fail, more extensive surgery should be carried out, which will be discussed under the next heading.

THE CANALICULI

Stenosis of a canaliculus is relatively common. It may be congenital or secondary to trauma, inflammation, or a foreign body (including concretions). Diagnosis of this condition is established by probing and radiography. Probing in an infant up to 12 months of age may be adequately performed as an office procedure, if proper assistance is available. Probing should be done, however, only by physicians who are thoroughly familiar with the anatomy of the system, as false passages can be readily made by the inexperienced. The probe should never be used with force. Syringing of the lacrimal passages immediately following the probing is contraindicated as the fluid may easily extravasate into the periductile tissues at the site of a small abrasion. Irrigation of the system should be carried out several days after the passage of the probe to check the maintenance of patency. Duke-Elder[1] states that "passage of the probe is so frequently successful that it is probably unwise to allow chronic changes to occur in the mucosa which may lead to trouble." Probing at the right time, in the right case, is very valuable, but it works immediately or not at all. Normally functioning healthy lacrimal passages are relatively immune to pathogenic microorganisms because of the resistance of the mucosa and the bacteriostatic property of the tears. Stasis promotes the development of infection and leads to secondary changes in the mucosa, cicatrization, and obstruction. Organic strictures can be demonstrated by radiography.[2] Their exact location as demonstrated by this procedure aids in the determination of the proper procedure to relieve the obstruction. If the stenotic canaliculus cannot be kept patent by probing, polyethylene tubing may be placed in situ.[3] Failing these methods, the more extensive lacodacryocystostomy should be considered. In this procedure a surgical communication is made directly from the lake of tears in the conjunctival cul-de-sac into the lacrimal sac, thus by-passing the canaliculus.

LACRIMAL SAC

The most frequently encountered clinical abnormality of this structure is the presence of infection. It may be unilateral or bilateral. Dacryo-

cystitis in infants is nearly always the result of pre-existing stasis with superimposed infection. The site of the obstruction is most often in the nasolacrimal duct; rarely a bony stricture may be responsible for the stasis. Simple blockage by epithelial debris in an anatomically normal system is not infrequent. Clinically the only evidence of stasis may be a pseudoconjunctivitis which may begin following birth, but more often appears between the third and sixth week of life, at which time tears are first formed. The course is typically mild and chronic, eventually leading to complete cicatricial obliteration of the lacrimal passages. A lacrimal system which harbors infection is potentially dangerous and can cause an intractable conjunctivitis, or is capable of making minor corneal abrasions develop into serious sequelae—ulceration with or without hypopyon and iritis.

Should infection develop within the lacrimal sac, it will subside spontaneously with the establishment of adequate drainage via the nasolacrimal duct. The best treatment of dacryocystitis is prophylaxis. Epiphora is the most important sign which precedes the development of frank infection. If the soft tissues are at fault, the treatment is dramatic if carried out before gross cicatricial changes take place. Early treatment, therefore, is of utmost importance. Conservative measures, such as the local use of antibiotics and massage for several months, permit changes in the mucosa to occur which may make the infective treatment more difficult later. The recommended procedure of choice is early irrigation by syringing of the obstructed lacrimal passages. The details of this technique have been adequately described in the literature.[4] If this is unsuccessful, it should be immediately followed by gentle probing to remove epithelial debris or make an opening in an imperforate membrane. Since a single probing is so frequently successful, it is best not to delay treatment beyond the age of 3 months. Serious complications from probing properly performed are practically nonexistent. Probing may have to be repeated, particularly in those indi-

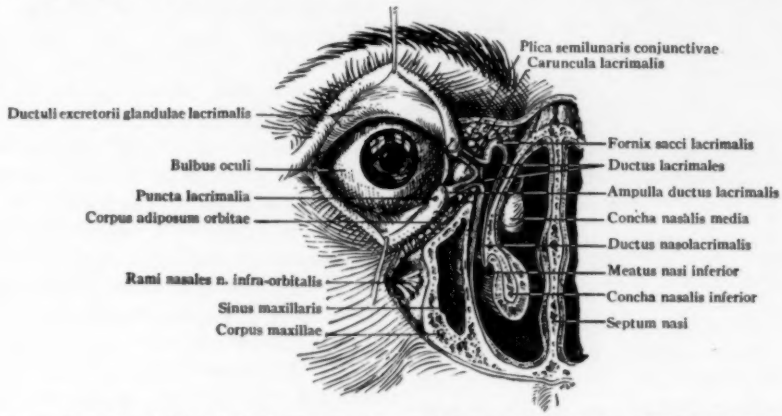

Fig. 1.—Anatomy of the lacrimal system. (From Anson and Maddock: Callander's Surgical Anatomy, W. B. Saunders Co.)

viduals who have been carried on conservative treatment for a long time. The rare individual in whom the obstruction is due to a bony deformity may require excision of the lacrimal sac or a dacryocystorhinostomy.

Fig. 2.—Frontal section, showing the persistence of the membrane occluding the inferior meatus of the lacrimal duct. (From Cassady, J. V.: Arch. Ophth., Feb., 1952.)

Unfortunately, textbooks in pediatrics have recommended in the past that conservative measures be employed until the age of 12 or more months.[5] This allows changes in the mucosa to take place, months of needless anxiety of the parents, and perhaps causes more extensive surgical procedures to be necessary than if the condition had received proper attention during the earlier months of life. Some of the newer editions, however, are now recommending earlier probing.[6, 7] If early probing is carried out, the busy pediatrician is no longer plagued for months because the conservative therapy has not been beneficial.

THE NASOLACRIMAL DUCT

The most common cause for epiphora is abnormalities of this portion of the lacrimal apparatus.[8] The two most common sites are the portion of the duct that joins with the lacrimal sac, and the site of exit into the nose under the inferior turbinate. There may also be congenital strictures, failure of canalization, blockage by epithelial debris, and inflammatory products. Probably the most common cause of epiphora is a thin congenital membrane at the junction of the nasolacrimal duct and the nasal mucous membrane. In 1950 a study of 1,000 unselected consecutive full-term infants reported an incidence of 5.7 per cent congenitally nonpatent nasolacrimal ducts.[9] The imperforate membrane may open spontaneously without probing, using only conservative measures, but if the duct is not patent by the second or third month, it is unlikely that the occluding membrane will rupture spontaneously. This form of occlusion can often be diagnosed and treated simultaneously by a single lacrimal irrigation. If the irrigation is not successful, it should be immediately followed by probing. In the infant the nasolacrimal duct passes downward and slightly backward and inward, whereas in the older child it has a more vertical course. Cassady[10] recommends early probing of the nasolacrimal duct. In his series of one hundred cases of dacryocystitis of infancy there was prompt clearing without incident or bad effect from this management. Only one or two treatments were required to cure the dacryocystitis which had existed several months prior to probing. In his experience, if probing is delayed until the infant is 6 months or older, the infected mucosa loses its elasticity and recuperative ability. Thus in these cases, it is more difficult to get

a response in one treatment than it is with those who seek help earlier.

If probing is unsuccessful, radiography studies can be made to determine the site of obstruction. In those cases in which repeated probing is unsuccessful, conservative measures should be carried out until the infant reaches an age at which time a dacryocystorhinostomy is considered practical. Blankstein[11] has reported that this surgical procedure in young children, as early as 18 months of age, is as successful as it is in adults. In any case of true epiphora, no surgery should be done on the lacrimal gland at any time.

SUMMARY

Epiphora has been defined and its varied etiology discussed. A plea is made for early diagnosis and immediate institution of therapy, preferably before the infant reaches 3 months of age. This opinion has been reiterated by numerous authorities.[12-15] Unfortunately too many physicians still delay active treatment for months. Conservative therapy is a nuisance and a constant source of anxiety to the parents. Although patients do respond satisfactorily to this management, it should not be continued for indefinite periods of time. To permit blockage of the lacrimal system to persist, allows secondary changes to occur in the mucosa. After no more than two months of conservative treatment without success, probing should be carried out immediately. Epiphora indicates stasis, and stasis predisposes to infection. Since infection about the eye is so potentially dangerous, it is unwise to assume this risk by delaying adequate relief of this condition. As pediatricians learn that dacryocystitis of infancy can be cured so readily, they will not prolong conservative treatment needlessly, but will send the infant to the ophthalmologist earlier.

CONCLUSIONS

Epiphora is more common than generally recognized. The advantages of prompt recognition of this important symptom and the various forms of treatment necessary have been discussed. A special appeal is made for early probing of the lacrimal apparatus before secondary changes in the mucosa occur.

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PROGRESSIVE DIAPHYSIAL DYSPLASIA (ENGLEMANN'S DISEASE)

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IN 1929, Englemann[2] first described a case of symmetrical fusiform expansion of the cortex of the shafts of the long bones in a child. Since that time eleven other cases have been reported. This is a report of the thirteenth.

The disease is a member of that group of sclerosing osseous lesions with no definite etiology which includes marble bones, melorheostosis, and osteopetrosis. Some clinicians would include osteopoikilosis in this group.

Most cases occur in children, although the range extends from 3 to 28 years of age. Both sexes are involved about equally. Clinically, all the patients appear undernourished. They complain of vague leg pains, poor appetite, easy fatigability, and a failure to gain weight. Muscle weakness probably contributes to the peculiar waddling gait noted in all reported cases. There is a rather striking disproportion in the size of the long bones with relation to the surrounding musculature. All patients have an average intelligence or better. Family history is noncontributory.

The roentgenograms show symmetrical, dense, fusiform cortical expansion of the diaphysis without trabeculation. This hyperostosis tends to obliterate the medullary cavity. The metaphysis and epiphysis are not involved by the process. The transition from the normal to the abnormal is rather abrupt and the progression is along the long axis of the bone. Most commonly the femurs and humeri are involved with the bones of the legs, forearms, and clavicles next. Quite frequently there is sclerosis in the base of the skull.

Ribbing[8] reports four siblings with multiple bones showing diaphysial sclerosis. The changes were not symmetrical. Also this appears to be a hereditary disturbance not seen in other reported cases. I do not believe his cases to be Englemann's disease and they are not counted in this report.

The differential diagnosis is primarily from *infantile cortical hyperostosis* which, as the name implies, occurs mostly in infants. They show fever, irritability, muscle swelling, periosteal reactions, and frequent involvement of the ribs and mandible. Recovery without residual change is the rule.

Osteopetrosis begins in the metaphysis, is hereditary, and shows dense involvement of both membranous and enchondral bone.

CASE REPORT

S. D., a 7-year-old girl, was first seen in December, 1950. At that time she was a puny, rather malnourished, underdeveloped, white girl with a peculiar waddling gait. She was complaining of bone pain. Clinically she

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was suspected of having syphilis. Serological tests showed no evidence of this.

Radiographically there was cortical thickening of the diaphysis of both femurs. Most of the involvement was in the upper third of the bone and heaviest on the medial aspect. A tendency toward lamination was noted which gave the appearance of periosteal elevation. The cortical proliferation encroached on the medullary cavity.

Fig. 1.

No evidence of other disease was found and she was given a tentative diagnosis of Englemann's disease. Periodic examinations and annual x-ray studies showed a progression of the cortical thickening until at this time the femoral medullary cavity is nearly obliterated in the middle one-third of these bones. In addition, there is involvement of the remaining long bones and clavicles. Films of the skull show sclerosis of the sphenoid, petrous portion of the temporal bone, frontal and malar bones.

Fig. 2.

Laboratory studies were normal save for a corrected sedimentation rate of 40. A bone and muscle biopsy was

Fig. 3.—X-ray, 1955.

Fig 4.—X-ray, 1955.

Fig. 5.—X-ray. 1955.

done. The bone fragment was difficult to decalcify and showed only sclerotic bone. Muscle tissue was normal.

SUMMARY

A case of progressive diaphysial dysplasia (Englemann's disease) is presented.

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Middletown in Monmouth County, October 26th, 1739. The Wife of one John Mackenster was brought to Bed of three Girls and all likely to live, being her first Children, and she upwards of 40 Years of Age, the Neighbouring Women of all Ages, both far and near come Daily to see them: And it is Thought there will be a great Discontent amongst the Marry'd Women that their Husbands can't Perform the same piece of Manhood.

NEW YORK WEEKLY JOURNAL, November 12, 1739.

ACUTE HEMORRHAGIC PANCREATITIS IN CHILDHOOD

J. Merrill Gibson, M.D., and J. Merrill Gibson, Jr., M.D.
Providence, R. I.

PANCREATITIS is an unusual condition in childhood. Cases may be divided into acute, chronic, and chronic relapsing. The acute cases may be further divided into acute interstitial and acute hemorrhagic. Cases may also be classified according to etiology into primary and secondary groups. The cause of primary pancreatitis is still unsolved, although it is generally considered to be due to obstruction in the ampullary region with reflux of bile into the pancreatic duct, or due to metaplasia of the lining of the pancreatic ducts, resulting in obstruction.[3, 5] Secondary acute pancreatitis has been reported following a number of causes. Mumps is probably the most common source in children. Other infections such as scarlet fever, typhoid fever, diphtheria, influenza, and otitis media may be complicated by pancreatitis either concomitantly or as sequelae. A review of the literature revealed only twenty-seven cases of acute pancreatitis of severe degree in childhood. Dobbs[2] was able to collect records of only fourteen cases occurring prior to 1935, and added one case of his own. Jaeger[4] in 1943 reported a new case of his own and added nine more cases found in the literature, not previously reported by Dobbs. Shallow and Wagner[6] reported a case following trauma. Shanks and associates[7] in 1954 added another case. Among the twenty-eight cases (including our own) there were fourteen deaths, giving a mortality of 50 per cent. Thus, although a rare disease, it is surely an important one.

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It is the purpose of this paper to report a case of acute hemorrhagic pancreatitis which was probably secondary to acute otitis media.

CASE REPORT

A 6-year-old white male was admitted to the Rhode Island Hospital on Dec. 12, 1954, with a chief complaint of abdominal pain. Approximately one month prior to admission he developed an earache, sore throat, and temperature of 38.3° C. He was treated with Gantrisin, 3 Gm. daily, for about ten days, with subjective relief, but temperature remained elevated at 37.6° C. Two weeks prior to admission he developed a cough and a heavy white nasal discharge. He was given no treatment for this. One week prior to admission he developed a temperature of 38.3° to 38.9° C., and purulent material was noted to be coming from a perforated tympanic membrane. He was again treated with Gantrisin and local medication into the ear. The temperature returned to normal and the aural discharge ceased. X-rays of the mastoid were normal. Two days prior to admission his temperature returned to 38.3° to 39.4° C. On the day of admission he began to complain of pain in the lower abdomen, and vomited about five times. The pain then shifted to the periumbilical region. He had two normal bowel movements on the day of admis-

sion. Past history was interesting in that he had had a feeding problem in infancy, the exact nature of which was not established but seemed to resolve spontaneously.

Physical examination revealed an acutely ill child with a temperature of 38.3° C., pulse 128, blood pressure 118/78. The ears showed no evidence of infection. The abdomen was not distended. There was generalized tenderness and rebound tenderness. There was some spasm of the recti, more marked on the right. There was also marked left CVA tenderness. On rectal examination there was tenderness throughout the pelvis. No masses were felt anywhere. White count was 41,500, with 92 per cent polymorphonuclears. Urinalysis was negative. It was felt that the most probable diagnosis was acute appendicitis, but because there was a considerable degree of doubt about the diagnosis, he was observed for about four hours, during which time his white blood count rose to 49,000, with 92 per cent polymorphonuclears. It was then felt that exploration could no longer be withheld and he was taken to the operating room.

Under open drop ether anesthesia a McBurney incision was made. On opening the peritoneum, cloudy fluid with specks of fibrin was seen. The appendix was normal and was quickly removed, and the incision closed. An upper right rectus incision was then made, since it was the operator's impression that this was either a perforated ulcer or a pancreatitis. The colon was lifted up, and multiple hemorrhagic areas were found intraperitoneally just distal to the hepatic flexure. A large, firm mass was felt in the region of the head of the pancreas. The lesser peritoneal cavity was entered by opening the gastrocolic ligament. The pancreas was found to be markedly swollen and covered with plastic exudate, and areas of necrosis and hemorrhage were seen. The entire organ was involved. Large lymph nodes measuring up to 2.5 cm. were found along the aorta and in the mesentery. A portion of the peritoneal fluid was taken for analysis for amylase, and the incision was closed.

A serum amylase drawn while the patient was on the operating table was 22 MK (Myers-Killian) units (normal 10 to 25). The peritoneal fluid contained 70 MK units of amylase. Urinary diastase on the first postoperative specimen was 58 units (normal 20 to 40). Four days later it had fallen to 39. Serum calcium on the fifth postoperative day was normal, 4.9 meq. per liter (normal 4.5 to 5.5). A repeat serum amylase was 16 MK units. Cultures of the peritoneal fluid were sterile. A mumps agglutination test performed one week postoperatively was positive in a dilution of 1:40. It is felt that this was due to a previous attack of mumps in that there was no clinical evidence of mumps in the two months prior to this acute episode. The patient was treated with constant gastric suction and parenteral fluids for forty-eight hours and then was placed on a low fat, high protein, high carbohydrate diet. His recovery has been excellent, but only time will tell if his disease will recur in a chronic form.

COMMENTS

There are several interesting aspects to this case. The association of the upper respiratory infection and otitis media to the onset of pancreatitis seems significant, and yet culture of peritoneal fluid revealed no organisms. Therefore it may be questioned as to whether there was actually any hematogenous spread of bacteria. The fact that the child had been a feeding problem in infancy, even though the cause was never established, causes some speculation as to whether some unrecognized disease of the pancreas may be a predisposing cause. This case, as most others reported in literature, was submitted to surgery with the presumptive diagnosis of ruptured appendix. The diagnosis of pancreatitis

could not have been established with a serum amylase for it was not elevated in a specimen taken within twelve hours of the onset of the illness or on subsequent testing. An interesting confirmatory diagnostic tool, namely the determination of amylase activity of the peritoneal fluid, is suggested. Had the index of suspicion been great enough, a specimen could have been obtained by paracentesis prior to surgery and an unnecessary operation could have been avoided. We have performed this procedure on two adults and established a positive diagnosis in the absence of an elevated serum amylase. The procedure is carried out under local anesthesia about two inches to the left of the umbilicus with a No. 18 short bevel needle. Air is injected just as the needle pierces the peritoneum to push the bowel out of the way. We have been able to obtain between 1 and 2 c.c. of fluid, which is adequate for amylase determination.

SUMMARY

1. A brief review of the literature on acute pancreatitis in childhood is given.

2. A case of acute hemorrhagic pancreatitis in a 6-year-old boy is reported.

3. Normal serum amylase but marked amylase activity of the peritoneal exudate were interesting findings.

4. A valuable diagnostic tool, abdominal paracentesis for amylase determination, is described.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

First Admission.—A 6-month-old baby girl was admitted to the hospital because of muscular hypotonia and retardation. The patient was born at term, the third child of a 31-year-old mother, whose pregnancy was complicated by pernicious vomiting and mild toxemia. Delivery was uneventful, and the neonatal period free of cyanosis or other difficulty. The parents were first cousins; the family history was otherwise negative. The infant was breast fed, gained weight adequately, and seemed healthy, save for noisy breathing until 5 months of age, when she developed intermittent fever, anorexia, and occasional vomiting. In addition, her breathing became noisier than usual.

Her physical activity up to that time had included only kicking of the legs and motion of the arms. She had never rolled over, nor raised her head. Pertinent physical findings on admission included good general nutrition, but a markedly hypotonic, weak attitude with sluggish deep tendon reflexes. The pupils were reactive; the fundi were not seen. Laboratory examination revealed pyuria with positive cultures for *Colobactrum coli,* a marked leukocytosis, and x-ray evidence of peribronchial inflammation. It was noted that "increased voltage was necessary to produce stimulation of muscles" by faradic current. Treatment with sulfapyridine, followed by sulfonamide, resulted in clearing of the chest but not of the urine. She was discharged against advice eleven days after entry.

At age of 1 year 2 months, Dr. Bronson Crothers' examination in the outpatient department revealed extreme general weakness, hypotonia, and absent tendon reflexes, with pallor of the optic discs. At age 1 year 8 months, he noted that she held up her head very poorly, but appeared to recognize her parents and occasionally smiled and said "mama." A year later, she could get on all fours and arch her back but did little if anything else. She continued, as always, to choke easily. No bowel or bladder continence had been achieved.

Second Admission.—She was readmitted at the age of 2 years 8 months for study. The pertinent findings were as follows: Good general nutrition in a dull, hypotonic infant lying in frog position. Reactive pupils but frequent nystagmoid "searching"

movements and pale discs. Marked hypotonia, with falling of head both backward and forward, legs hanging limply, and absent tendon and abdominal reflexes. She occasionally followed light with her eyes and seemed to hear loud noises. The respirations were, as always, noisy.

Laboratory examinations revealed normal urine and hemograms, a cerebrospinal fluid with a total protein of 17 mg. per cent, and negative Hinton and Wassermann tests. Pneumoencephalogram revealed minimal, symmetrical enlargement of lateral ventricles and somewhat prominent subarachnoid pathways, but an essentially normal pattern.

At age 5 years, she had developed some athetoid movements of the upper extremities, which had progressed when seen at age 7 years. She had continued to be helpless, without speech or continence.

Third Admission.—At age 12 years she was admitted for extraction of abscessed teeth and had continued to be completely helpless, had developed no speech, and appeared to grasp little of what went on about her. Tonic neck reflexes had been seen transiently. Pertinent findings at age 12 years were those of an emaciated, unresponsive, helpless girl who showed constant facial grimacing, rolling of the tongue, drooling, sustained lateral nystagmus, and athetosis of the arms, with some spasticity of the forearm muscles. The legs were completely flaccid and areflexic, while the tendon reflexes of the upper extremities were present, though diminished. Abdominal reflexes were active. Pupils were unreactive. The only additional findings were two abscessed lower molars. Laboratory examination revealed a 1 plus albuminuria with 3 to 5 leukocytes per high-power field on a noncatheter specimen. The urinary infection was cleared with penicillin, and the abscessed teeth were extracted uneventfully.

During the following year she was committed to a state institution, where she died at 13½ years of age.

DISCUSSION

DR. SIDNEY FARBER.—I am very happy today to welcome back for a return engagement, Dr. Joseph Foley. You will recall his instructive session of not long ago. Dr. Foley has complete freedom to talk as a clinician first and then correct the pathologic diagnosis, if he will, when that is given by Dr. Craig. Dr. Foley is assistant professor at Harvard and is the neuropathologist at the Boston City Hospital.

DR. JOSEPH FOLEY.—Thank you, Dr. Farber. As I entered the room today I was met by Dr. Farber who said, "I hope you can help us on both ends of this case." I was then met by Dr. Crothers who scratched his head a little bit and said, "I hope you can help us with this case." It is perfectly clear to me that I am a sacrificial lamb on the altar of the ignorance to Boston neurology. Let me say, in advance, that Dr. Crothers has moving pictures of the child and to a neurologist that is worth a thousand words of description. The only thing better than the film is the living specimen walking or trying to walk in front of one. I well remember, it is now many years ago, when I first heard about pediatric neurology from the lips of Dr. Crothers and he taught me

something at the time that I have been teaching ever since, namely, that the neurological examination of the infant is best accomplished by leaning on the edge of the crib, cupping one's chin in one's hand and watching the child for at least twenty to thirty minutes before attempting to lay on hands. I have followed Dr. Crothers' advice precisely over the years. The trouble is that I still do not know what to watch for. I regret that my contact with him was so slight back in those days.

Let me say in advance that I have no notion of what is wrong with this child in the sense of an etiological diagnosis, or of a name for the pathological process. I can only say I believe this is a widespread, diffuse derangement of the central nervous system involving predominantly the motor elements, particularly the anterior horn cells of the spinal cord, the large motor cells, probably of the medulla and the pons, with a diffuse affection of the cerebral cortex and the subcortical gray matter. That, in effect, is my diagnosis. The etiology, I think, is unknown to me, from the clinical point of view, and my small experience with such suggests to me that it probably is going to be unknown to the pathologist. By etiology, I mean the cause of the structural lesion.

I think it is instructive in a clinicopathologic conference to handle it, not as if it were a jigsaw puzzle, not to anticipate things too far, but to try to work ourselves back in time and perplexity to the problems of the person who was following the patient. The chief complaint given by the family of this child was muscular hypotonia and retardation, as nonspecific a pair of symptoms as one can be presented with, I suppose, in neurological medicine. Muscular hypotonia is an important symptom. The slack child may present, early in his development, as a consequence of disease of the spinal cord, of muscle, or of mental retardation of the sort that even the pathologist is unable or unwilling to classify.

The family history gives some evidence of consanguinity. Consanguinity, however, in this case is not very helpful to me, particularly since we learn in the present illness that this was the third child of a relatively young mother and that the other two children were normal. Pernicious vomiting and toxemia complicated the pregnancy, and how much to make of that is difficult to say. The fact is that the child was born at full term, and we know that many normal children emerge from pregnancies complicated by pernicious vomiting and mild toxemia. Therefore, I think, from an etiological point of view this is not very helpful. And now we begin to wonder, because the physician confronted with this problem at this stage asks himself, "Am I dealing with something that arose after birth or am I dealing with something that arose before birth?" If the symptoms arose after birth, as a consequence of a process that began after birth, our chances of establishing an etiological basis are far greater than if the process began prenatally. We find, however, that the child did have one symptom right from the very beginning—the symptom of noisy breathing. I would view with deep suspicion the child whose mother has had two previous children and complains even a little bit that the child was breathing noisily. Therefore, I would keep in the back of my

mind the possibility that this went back at least to the time of birth, and that the pathologic process probably preceded birth. The child, however, seemed healthy until about 5 months of age, when, again, nonspecific symptoms appeared—intermittent fever, anorexia, and occasional vomiting. Again, these are symptoms that are not going to aid us in establishing an etiological diagnosis, except that the breathing became noisier than usual and she was admitted to the hospital for the first time at the age of 6 months.

A child who has noisy breathing has either trouble with the respiratory apparatus, per se, or perhaps has a cardiac disorder; but failing these it is possible that the disturbance is in the innervation of the mechanism of respiration. We find at the age of 6 months that her development had not attained what we might well expect of a 6-month-old child. She presumably had made no effort to do so. She kicked her legs. Did the legs seem strong? Did she kick vigorously? Did she move her arms vigorously? This we do not know but perhaps we will find out from Dr. Crothers' films. The clinical picture is now dominated by hypotonia. The cause of the intermittent fever, anorexia, and vomiting probably was eventually cared for. It was noted, however, that "increased voltage was necessary to produce stimulation of muscles" by faradic current. The details of that are lacking, and I am glad they are because I would have to look them up. In a way it is regrettable that we neurologists have lost our original function. The first neurologists at the Massachusetts General Hospital and at the Boston City Hospital were not dignified with the name neurologist. They were called, instead, "electricians." Simple electricity, however, has been lost sight of by the modern neurologist, including myself. The modern neurologist distrusts any kind of electrical apparatus that does not have four preamplifiers with four-power amplifiers superimposed on it. However, this simple reduction of reaction to faradic stimulation is extraordinarily helpful and we could probably properly return to using it, because the inadequacy of response to faradic stimulation suggests that there is incomplete motor innervation of the muscles concerned. This strongly suggests, therefore, the likelihood that we are dealing with a lesion in the lower motor neuron, at least in part. Students always arch their eyebrows when some of us mention the word lower motor neuron lesion because, as you know, the newer physiology in the last ten to fifteen years has destroyed the concept. I would say that it has destroyed the concept in the monkey, the cat, and the cockroach, but it still is a very valid concept for man. By a lower motor neuron lesion I mean a lesion of the anterior horn cells or a lesion somewhere distal, from the anterior horn cells down into the innervated muscles.

There were some weighty problems that must have arisen at this time. At this stage the practical physician asks himself: first, is it possible that this child has anything wrong with the central nervous system that can be specificially treated? We have a child who, even at this stage in the game, shows clearly some evidence of retardation in motor development. It may be that the child also shows retardation of psychologic development.

At that stage, however, the integrity of sense perception and of motor performance must be guaranteed before we can say anything about the integrity of intellectual capacity. And, therefore, I would guess that your neurologist hedged somewhat and said, "We are not sure at the moment whether this child is defective in the sense of being mentally retarded." I think I should have said, "I suspect it strongly, but I am not sure." Are there any remedial possibilities, however, in terms of the motor disorder? I suppose the only diffuse muscular derangement of early childhood about which we know anything concerning the specific management or treatment is myasthenia gravis. Is it possible that this child had myasthenia gravis? It is very likely. The symptoms and signs of myasthenia gravis are somewhat different. Hypotonia, associated with hypotonia in myasthenia gravis, is likely to be proportional to reduction of strength. In this child there was reduction of strength rather out of proportion to the hypotonia. There was no particular predominance of weakness of ocular movements, and no ptosis. There was no history of myasthenia in the mother, and, indeed, this weakness persisted without any of the alterations that we regard as characteristic of myasthenia. Therefore, I think, the pediatrician at that point probably said, "I do not know what is wrong with this child, but I do not believe this child has a specific disorder for which we have any specific treatment."

The next practical question is, "Is this a familial derangement?" This is important because one must make some estimate of the likelihood of affection of the other children. Not knowing what the disease process is, however, I think the physician at that time was unable to say whether this was a familial disorder. All he could say was that one out of three children had developed it. The likelihood that the other children would develop it, therefore, is not great. Would any future children develop it? We cannot say until we know what it is. The third question, and a practical one, is "How long is this child likely to go on?" Families want to know this. We assume that this child is not going to amount to very much from the sense of motor performance or of intellectual capacity. I think I would have been very unoptimistic about the chances for this child. At the age of 1 year 2 months Dr. Crothers saw this patient and he found again extreme general weakness. Pallor of the optic discs was present. If any less an observer had said that there was pallor of the optic discs I would have said nonsense. Pallor of the optic discs is one of the most frequent findings written down on a chart when it has no particular contact with reality. My guess would be that when seen at 1 year 8 months of age Dr. Crothers concluded that the child was mentally retarded, but I do not know. I would have thought so. This I would think represents, at this stage, therefore some intellectual retardation. We also have now a lower motor neuron lesion, suggestive of anterior horn cell or at least motor cell involvement. We have involvement of the optic discs, suggestive of a white matter affection of the brain. And we have the likelihood of mental retardation suggestive now of white matter instead of gray matter. Why do you not say a diffuse involvement? I believe this is not a neuronal

disease because almost nowhere up to the age of 2 years were there any convulsive disorders, and no myoclonus or myoclonic jerks. Therefore, I am more inclined to think that this was a subcortical derangement; and not in the cerebral hemispheres, at least, a progressive neuronal degeneration. Then, in another year, she could get up on all fours, but she did little if anything else. And, as always, she choked easily. Why did she choke? She could choke, of course, on the basis of the lower motor neuron derangement, or on the basis of the pseudobulbar palsy related to bilateral lesions of the cerebral hemisphere. Perhaps she was choking as much as she did because, indeed, she had a combination of the two. And she had, at that age, no bowel or bladder continence at all. A child at that age should at least have made a gesture in that direction; that is very reassuring to a parent. At 3 years of age she again displayed marked hypotonia, inability to hold the head up, with legs hanging limply, and with absent tendon and abdominal reflexes. She occasionally followed light with her eyes and therefore it is possible that she was seeing something. She seemed to hear loud noises but her level of performance was such that even a skilled observer could not be sure. The pneumoencephalogram was equivocal.

At the age of 5 years she developed athetoid movements of the upper extremities. If someone says "athetoid," I ask myself, what does he mean; is it or is it not athetosis? I am interested in these athetoid movements particularly, because they implicate still another system. If there are athetoid or athetotic movements, and especially if there are choreoathetotic movements, then, I think, we can postulate that there is involvement of the basal nuclear structure. If the combination of chorea and athetosis exists then I think there is a high presumption of involvement of not only the basal nuclear structure, but of the cerebral cortex and underlying white matter as well. I think that is the difference between athetosis and choreoathetosis. Athetosis may mean a fairly well localized disorder of the basal nuclear structures, whereas choreoathetosis means a more widespread involvement of the cerebral hemispheres, including the basal structure.

DR. JOHN M. CRAIG.—Would you give your definition of choreoathetosis?

DR. FOLEY.—First of all, I regard chorea as a sudden, violent, rapid displacement at a single joint. Athetosis, on the other hand, is a slower alteration of movement at several joints, so that the child with athetosis extends and flexes, or he pronates and he supinates. The child with Sydenham's chorea, I suppose, best exemplifies chorea, and the patient with double athetosis, without chorea and with intact intellectual structure best represents the state of athetosis.

The situation went on to the age of 12 years, when everything became worse, and something else entered the picture. In addition to the evidence of a lower motor lesion, of a white matter lesion of the brain, of a diffuse gray matter lesion of the brain, we now have spasticity. Spasticity indicates that there is bilateral derangement of a particular part of white matter, namely, the cortical spinal tract. Therefore, we find that

as this clinical history unfolds itself there unfolds with it increasing evidence of involvement of all parts of the nervous system except, possibly, the sensory apparatus. And that is what I would expect to find pathologically in this child. I would expect to find that there was widespread loss of the anterior horn cells, widespread loss or reduction of motor cells in the pons and medulla, and loss of cells, probably with replacement gliosis in the basal nuclei, including the thalamus. I would expect also that there would be demyelinization in the cerebral hemispheres, as well as atrophy of the cerebral cortex. I anticipate that there will be no pathologic signs that will allow us to arrive at anything but an anatomic diagnosis. I think we can surely say that this had no relationship to trauma because of its diffuseness, and that this had no relation to infection, again because of its diffuseness. From the distribution, we probably would be able to say that this represents a metabolic disorder, occurring prenatally, cause undetermined, cause unknown, and no way at present of finding out.

DR. FARBER.—Thank you, Dr. Foley. Dr. Crothers, would you like to take the podium?

DR. BRONSON CROTHERS.—This child, from my point of view, was always an extremely limp child. She was referred originally as an amyotonia congenita, which to some extent she had, if that satisfies anyone. I felt from the very start that the child was defective, from the time she was 1 year old. I think it is worth noting in the moving pictures that this child is crying hard and I do not think you can get a normal child to relax that much while crying. One can see there irrelevant and constant activity. I think the evidence that appealed to me was the character of the activity, the progressive signs in the eyes, and the maintenance throughout of this hypotonia.

DR. FOLEY.—I would like to say that I avoided the diagnosis of amyotonia congenita deliberately because I do not really regard it as a diagnosis. And, if I remember, Dr. Crothers feels the same way. It is rather a state into which a child may get as a consequence of many different diseases. It may represent a disease of the lower motor neuron, but probably not always so. It conforms to no established pathologic entity.

DR. CRAIG.—I would like to ask Dr. Foley or Dr. Crothers how frequently they see cerebral patterns of this type combined with marked hypotonia? I have been loking it up in textbooks and it does not seem to be very common. I wondered if that was their experience.

DR. FOLEY.—The man with the lesser experience speaks first, I guess. I have never seen it, Dr. Craig. But the fact that I have never seen it does not mean that it does not exist, of course. If neurological reasoning means anything, I would like to think that it does. I think it must mean, therefore, that this child has lesions at all levels, all the way up. I do not believe a child could ever be this hypotonic for a good number of years because of lesions in the cerebral cortex alone, or with a progressive neuronal degeneration alone. I think this degree of hypotonia, persisting

over such a long period of time, must mean that there is involvement of the lower motor neuronal system as well.

DR. FARBER.—Dr. Crothers.

DR. CROTHERS.—I think the number of times that we have seen limp babies who later developed athetoid and other patterns is very considerable. Of course, the classic combination of limpness and neurological disease above the spinal cord level is Tay-Sachs disease, where at one time the babies are completely and solely limp and then become stiff and so on.

The amyotonia has bothered me enormously. We have been wrong almost continuously in trying to make it into a disease. The familial incidence of so-called amyotonia as against Werdnig-Hoffmann's disease is deceptive, and some progress and some do not; but the combination of these cerebral symptoms with hypotonia, I should think, is rather common, although I have never seen a child just like this.

DR. FARBER.—Dr. Osborne, would you tell us the discharge diagnosis or diagnosis at any time along the course?

DR. MAURICE OSBORNE.—The diagnosis at the time of the original admission was probable amyotonia congenita.

DR. FARBER.—Dr. Craig, would you give your findings.

DR. CRAIG.—The reason this case was chosen, I think, was that it represented a case in which there was some element of cerebral palsy and in which the pathology department was fortunate enough to be able to demonstrate lesions. Also, the problem of amyotonia was an interesting one to us.

We are indebted to Dr. Paul I. Yakovlev for preparation of the brain tissues and in part for the interpretation. The cortex of the brain showed a good deal of disorientation of the neuronal ribbon (Fig. 1), which was thicker than normal. The cellular pattern was markedly disturbed. In addition, in the cerebral white matter there was a pattern that is known to the neuropathologist as status marmoratus (Fig. 2). It consists of a "marbling effect" in the areas of the gray and white matter, with marked unevenness in the distribution of the myelin pattern, with extension of the myelin sheaths into the subcortical gray masses. In the subcortical white matter we were able to demonstrate a marked change in the neuronal cells of the substantia nigra (Fig. 3), though no marked gliosis was present here. Similarly, in the dentate nucleus there was almost complete absence of neuronal elements. In the spinal cord there was no evidence of degeneration or failure of the myelinization. However, in the gray matter, especially in the lateral horn, there was marked degeneration of the neuronal cells and glial pattern (Fig. 4), most marked in the lumbar and upper sacral regions. In all of the eight or nine sampled areas of the peripheral muscles there was much atrophy of the muscle fibers, with a few large muscle elements persisting among numerous small and atrophic fibers (Fig. 5). We were also able to demonstrate atrophy of the peripheral nerves.

The immediate cause of death was an acute bronchopneumonia. We are able therefore to correlate the failure

Fig. 1.

Fig. 2.

Fig. 1.—Temporal cortex. There is marked disorientation of the neuronal ribbon. (Cresyl violet; ×45; reduced ⅛.)

Fig. 2.—Temporal cortex. There is an extension of the myelin sheath structures into the neuronal ribbon. (Pal-Weigert; ×30; reduced ⅛.)

Fig. 3.

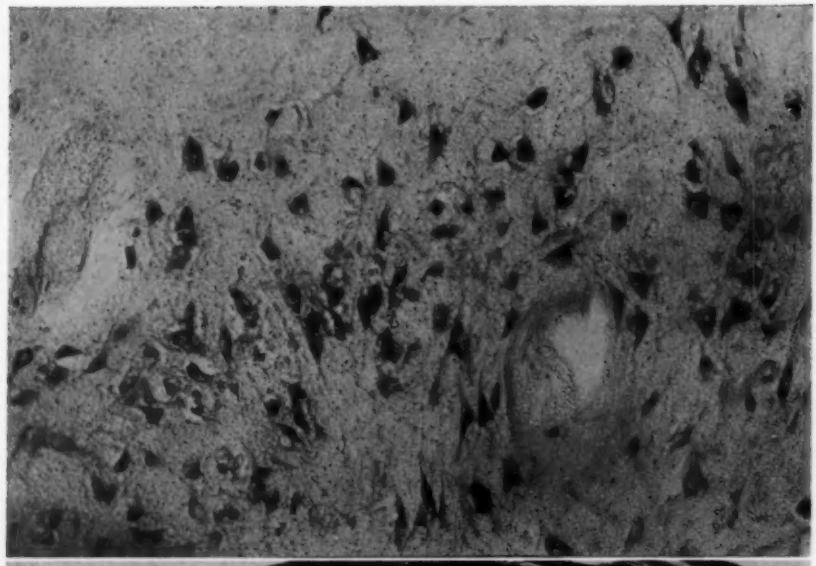

Fig. 4.

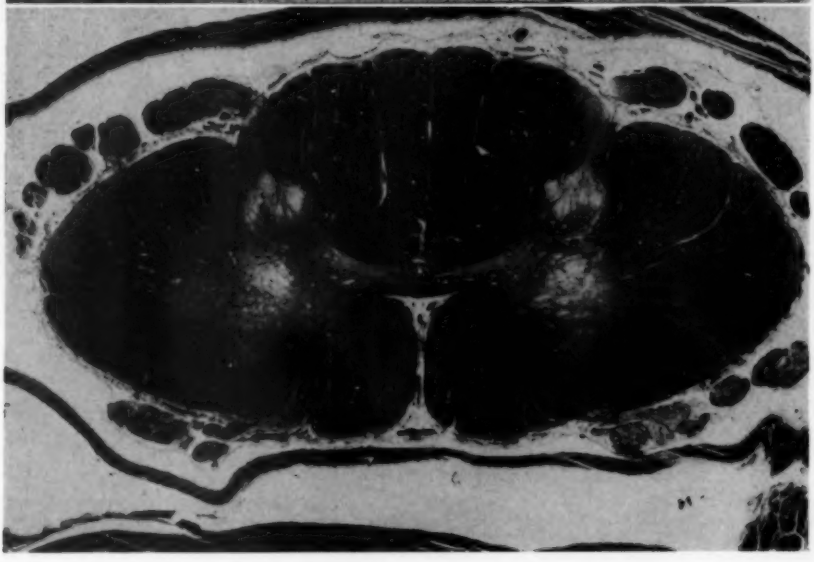

Fig. 3.—Substantia nigra. Degenerative changes are present in the neuronal cells. Little gliosis is present. (Cresyl violet; ×135; reduced ⅛.)

Fig. 4.—Cervical cord. A symmetrical loss of the glial net is seen in the mid-zone of the gray matter. No tract degeneration is present. Less myelin is demonstrable in the anterior than the posterior nerve roots. (Pal-Weigert; ×12; reduced ⅛.)

of intellectual and psychologic development with the alterations in the neuronal pattern of the cerebral cortex and subcortical white matter; the choreoathetosis, with the alterations in the basal ganglia of the cerebrum and cerebellum; and finally the marked hypotonia, with the atrophy of the peripheral nerve and muscles, a lesion which is associated with atrophy of neuronal elements in the spinal cord.

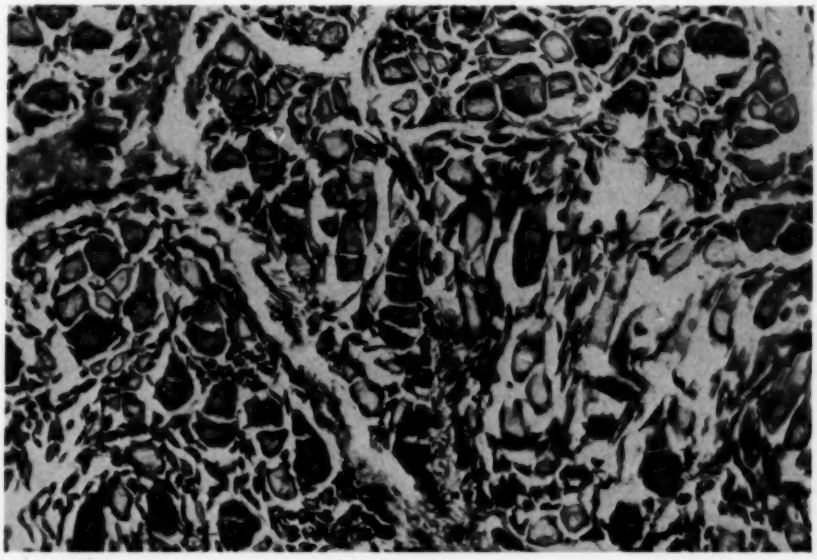

Fig. 5.—Voluntary muscle. Marked variation in size of muscle fiber is present. (H & E; ×270; reduced ¼.)

As Dr. Foley predicted, we do not have an etiological diagnosis in this case, but we agree with him that it represents the end result of an alteration taking place fairly early in antenatal life.

Dr. Foley.—The problem of status marmoratus is a very complex one. I think there are a couple of facts, however, that are quite clear about it and one is that status marmoratus occurs at the time that myelin is being laid down. Second, that it does not occur from the lesion beyond the period of myelogenesis. Myelogenesis, as you know, may continue until the second or third year of life, possibly, and therefore theoretically at least status marmoratus may appear at any time in this period. I do not believe that status marmoratus is ever found in the presence of any otherwise intact neuronal apparatus. The present thinking about status marmoratus is that it represents a situation in which the glia get bound up in the process of reparation of the nervous system. If it has not already been done, probably one of the most constructive things to do in this case would be to try to stain the axis cylinders, because I have the feeling that the number of myelin sheaths are all out of

proportion to the number of axis cylinders. The axis cylinders will, in fact, be reduced in the areas of status marmoratus, indicating again that this is an abnormal scar formation that has bound up the glia rather than anything else. I would have thought also that there was gliosis in the substantia nigra. I would not know where to classify this. I think some people would call this amyotonia congenita with cerebral disorder in which I think they would merely be classifying according to name, that is, not classification according to idea.

Medical Progress

SHOULD PRIMARY TUBERCULOSIS IN CHILDREN CONTINUE TO BE NEGLECTED?

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TERMINOLOGY

THERE has been much confusion of the terminology in the medical literature for primary tuberculosis. In this discussion, the term "primary tuberculosis" refers to a primary tuberculous infection which is evidenced by a positive tuberculin reaction, but, as a rule, without clinical evidence of illness in the child. Under certain conditions, the infection may mature to clinical disease within a short period of time. For instance, tuberculous meningitis, miliary tuberculosis, and progressive primary tuberculosis usually occur within a few months following the primary infection. Bone and joint tuberculosis usually develops within one year.[1, 11] These early sequels of primary tuberculous infections are referred to in this paper as "postprimary complications."

Chronic pulmonary tuberculosis is a remote but serious sequel of primary tuberculosis. This condition is seldom seen before the age of puberty. It is the most common form of reinfection-type tuberculosis seen in adult life. The time interval between the primary infection and chronic pulmonary tuberculosis varies from several years to several decades. However, when primary tuberculosis occurs during adolescence it may lead to chronic pulmonary tuberculosis within a short period of time.

The relationship between the subclinical tuberculous infection and the clinically manifested tuberculous disease is illustrated in Fig. 1. The latent infections are depicted as submarines hidden in the depth of the sea. Although out of sight, their presence is a constant threat to safety, because the torpedoes they carry may explode at unexpected moments, causing serious destructions. In the same manner is the latent tuberculous infection potentially dangerous to health, because it may be provoked to overt disease in unexpected times during a person's life.

I. SOME IMPORTANT FACTS ABOUT PRIMARY TUBERCULOSIS

Primary Tuberculosis, a Fountainhead of Tuberculous Diseases.—There are millions of children in the world today infected with tubercle bacilli. These children will constitute a significant portion of adult tuberculosis of tomorrow. Even if by some miracle all tuberculosis in adults could be eliminated from the world today, the

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world would not remain free from tuberculosis for any great length of time. As the millions of infected children grow up, many of them will break down with active tuberculosis and plague the world once again with the disease. They will in turn infect their children, and so the vicious circle will continue. Primary tuberculosis in children today is the fountainhead of adult tuberculosis of tomorrow. As long as tuberculosis in childhood is neglected, man cannot break loose from the grip of the menace of this disease and tuberculosis will continue to incapacitate and destroy useful lives generation after generation.

Aside from the more remote dangers mentioned above in the adult life, primary tuberculosis also causes serious diseases in childhood. Such conditions as tuberculous meningitis, miliary tuberculosis, and caseous pneumonia are the most common forms of tuberculous diseases in children.[1]

The early and the remote dangers of primary tuberculosis are graphically presented in Fig. 1.

The horror of white plague in children has not diminished in most parts of the world today. Tuberculosis still kills and cripples so many children that it remains one of their greatest menaces in many countries. I recall vividly how, in one such country, pediatric wards were frequently crowded by large numbers of children suffering from serious forms of tuberculosis. Cases of meningitis and miliary tuberculosis were so numerous that many of the patients died at home without adequate treatment.

The pediatricians in many parts of the United States do not see the grim picture of tuberculosis in children nearly as often as pediatricians in many other countries. This is because the United States is one of the few countries in the world today where much progress has been made in the control of tuberculosis by public health measures. However, the toll from tuberculosis in children is still high in some parts of this country. Available figures in the state of Texas reveal that from the years 1950 to 1953, 376 children under the age of 4 died of tuberculosis. In the same period of time there were 222 deaths due to polio, 123 due to heart diseases and 100 due to renal diseases in the same age group.[2] These statistics show the seriousness of tuberculosis in children even in this era of chemotherapy.

Primary Tuberculosis, a Neglected Disease.—The complacent attitude of the medical profession toward primary tuberculosis is evidenced by the paucity of writings on this subject in the current medical literature. Due to the absence of symptoms in the majority of children with primary tuberculosis, this phase of the disease has been mislabeled "benign," and therefore received little medical attention and interest. Too often when a case of adult tuberculosis is found, attention is concentrated on the adult. The children who have been in close contact with the tuberculous adult, and therefore probably infected, receive little medical attention. Pediatricians, in general, show so little interest in primary tuberculosis that routine tuberculin testing has become a neglected practice. As a result many children pass through clinics or doctors' offices with an undiagnosed primary tuberculosis. Devastating complications such as tuberculous meningitis, caseous pneumonia, and tuber-

culosis of bones and joints may happen without much warning. Neglect of primary tuberculosis in children often results in unnecessary delay in the diagnosis of these serious conditions, and not infrequently this delay means crippling or death of the child.

Many children who escape major complications of primary tuberculosis are able to wall off temporarily the tubercle bacilli which may be seeded in various parts of the body. This, however, should not lull us to the illusion that primary tuberculosis is an innocent disease, because all too frequently more trouble is to come. The walled-off foci are like bombs in the body which may explode to become the fountainheads of clinical tuberculosis in adult life. This completes the vicious circle of tuberculosis in human beings.

Fatalistic Attitude to Primary Tuberculosis, Result of Lack of Effective Therapy.—Until recently there was no therapy which offered promise for the treatment of primary tuberculosis. Whether the condition will remain dormant or will blossom forth to clinically active disease is entirely unpredictable. It is common experience to have known children who appear perfectly healthy until the sudden onset of tuberculous meningitis or miliary tuberculosis. In the past, because of the lack of effective therapy to control the course of primary tuberculosis, its outcome had been resigned to fate. As a result, physicians over the years have developed a fatalistic attitude toward primary tuberculosis, or a total disregard of its significance.

The advent of streptomycin did not change the situation materially because its value in controlling primary infection has been doubtful. For example, such serious postprimary complication as meningitis has been known to occur in children under streptomycin therapy. Because of this and the inherent toxicity of streptomycin, its use has been limited to cases where primary infection has already evolved to clinically manifest tuberculous disease.

It is fortunate that the new era, with the promises of effective antimicrobial drugs for tuberculosis, is bringing to a close the era of fatalistic attitude.

The Advent of Isoniazid Marks a New Era.—Since the discovery of isoniazid in 1951, experimental work and clinical trials have proved it to be a very effective drug in the treatment of tuberculosis. To date, accumulated data warrant serious consideration of its use in primary tuberculosis. It is only logical to treat an infectious disease at the earliest possible moment because in an early stage of an infection the drug is most effective in bringing about a cure. In the late stages, tissue destruction and other secondary changes due to chronicity of the disease usually complicate the therapeutic problem to such an extent that it makes a cure difficult and often impossible. For example, no one would doubt the wisdom of applying effective antimicrobial therapy to primary syphilis because it is generally realized how ineffective it is to treat syphilis in its late stages. On the other hand, secondary and tertiary manifestations of syphilis seldom occur if the infection is adequately treated in its primary stage.

As mentioned above, antimicrobial therapy heretofore has been used almost entirely on clinically manifest tuberculous diseases, while, the pri-

mary tuberculosis, which is the fountainhead of tuberculous diseases, has been left untreated. It is the purpose of this paper to stimulate some thinking in regard to the application of isoniazid therapy to primary tuberculosis before it has a chance to develop clinical manifestations.

In the interest of better understanding of the over-all problem, certain facts concerning the natural history of primary tuberculosis in the human body merit consideration, because these facts indicate the method required for the effective treatment and control of tuberculosis.

Natural History of Primary Tuberculosis in the Human Body.—Primary tuberculosis is by no means a localized disease, but one which is frequently disseminated to many parts of the body. It has been demonstrated in experimental animals that within a few hours of subcutaneous infection, virulent tubercle bacilli may be widely disseminated throughout the body.[3] The Ghon complex is but one part of this widespread infection. In the human being the infection is very active during the first few weeks, at which time the bacilli multiply so rapidly that great numbers of them can be demonstrated in the primary focus as well as in regional lymph nodes. Many of the bacilli find their way into the lymphatic channels and the blood stream and become deposited in various tissues of the body. Such metastasis is evidenced in the human body by the frequent finding of tubercles in the distant organs. It has been noted that the age of these metastatic tubercles corresponds to the age of the primary complex. When a body contains a fresh primary complex these metastatic foci are likewise fresh in appearance, which indicates that the dissemination of the bacilli takes place during the primary infection stage.[4]

Clinically, the existence of the widespread metastasis of primary infection is evidenced by such conditions as tuberculous meningitis and tuberculosis of the bones and kidneys. Tuberculosis in these organs is, in all probability, endogenous in origin. Recent study by culture of the human bone marrow revealed that tubercle bacilli could be demonstrated in 23 per cent of the recent primary infections.[5]

Recent pathologic investigations have revealed the fact that tubercle bacilli may remain alive and virulent in and about the primary foci for many years and even throughout the lifetime of the individual.[6] The usual healing process of tuberculosis, such as fibrosis, hyalinization, and calcification, cannot be counted on to wall off the infections permanently. The fibrous capsules surrounding the foci may break down and set free living bacilli. A calcified focus is often found to be but part of a caseous mass. Therefore what appears to be a calcified lesion at x-ray examination may actually, on pathologic examination, be a caseous mass containing calcium deposits.

Clinically, the fate of the primary complex and its metastatic foci varies a great deal as indicated in Fig. 1. They may progress to clinically manifested diseases within a short period of time, but some infection may remain dormant for years or even decades before breaking down with active disease, still others may remain latent throughout the lifetime of a person.

It appears that in a state of health the human host and the tubercle bacilli exist in a state of equilibrium. When

the balance is upset, active disease ensues. Clinical observations suggest that a number of factors may provoke a latent infection into an active disease. For example, the time relationship of menarche and the development of active tuberculosis in adolescent girls is a well-known fact. That malnutrition brought about a sharp rise in the incidence of tuberculosis has been observed time and again in history, there is ample pathologic evidence that reinfection type of chronic pulmonary tuberculosis and extrapulmonary tuberculosis such as seen in the adult is often the result of reactivation of primary tuberculosis or its metastatic seedings acquired at some previous time.[10]

As stated before, primary tuberculosis is most active during its early stage when the tubercle bacilli multiply

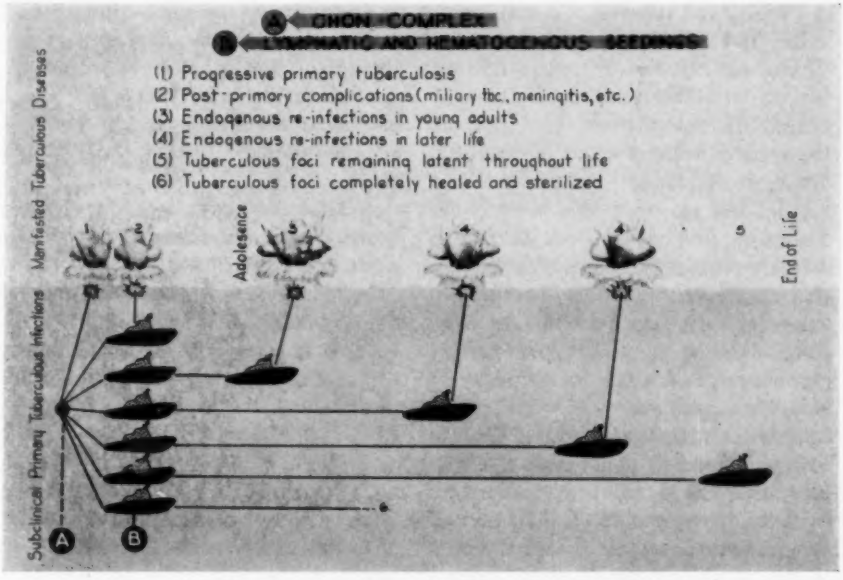
A GHON COMPLEX
B LYMPHATIC AND HEMATOGENOUS SEEDINGS
(1) Progressive primary tuberculosis
(2) Post-primary complications (miliary tbc., meningitis, etc.)
(3) Endogenous re-infections in young adults
(4) Endogenous re-infections in later life
(5) Tuberculous foci remaining latent throughout life
(6) Tuberculous foci completely healed and sterilized
Subclinical Primary Tuberculous Infections
Manifested Tuberculous Diseases
Adolescence
End of Life
A
B

Fig. 1.—Diagram showing the possible consequences of primary tuberculosis and its subversive nature and destructive potentialities.

tory.[7] Many acute infectious diseases in childhood, notably rubeola, causing flare-ups of latent tuberculous infection are the common experience of pediatricians. Recently the use of ACTH and cortisone has been known to cause exacerbation of arrested tuberculosis.[8, 9]

Although the factors which cause the reanimation of an apparently arrested primary tuberculosis are not well enough known and need more

rapidly in the body. The regional lymph nodes are markedly swollen and often form large caseous masses in the mediastinum. Active infections are likewise found in the metastatic foci in the various tissues of the body. During this time the infections are often manifested as active diseases. Because these disease conditions usually occur shortly after the onset of primary infection, they are, in fact, postprimary complications. The

severity of these complications and the frequency in which they occur vary widely from community to community, depending upon the local tuberculosis situation. According to Lincoln,[1] there are four major complications which account for 95 per cent of the deaths due to tuberculosis in children: (1) tuberculous meningitis; (2) miliary tuberculosis; (3) more protracted forms of generalized hematogenous tuberculosis; (4) locally progressive tuberculosis with cavitation and bronchogenic spread.

Clinical experience and follow-up studies of Wallgren[11] and Lincoln[1] proved that the great majority of these complications occur during the first year of primary infection. When a child has survived this period successfully, he has passed the most dangerous stage of primary infection.

A number of infectious diseases are more fatal to young infants than to older children. For example, pertussis, measles, and a number of pyogenic infections are much more serious in infants than in older children. Tuberculosis is no exception. Although primary tuberculosis has been assumed by some to be a benign condition, such generalizations certainly cannot apply to the primary tuberculosis in the infants. The characteristics of the disease in this age group are rapidity of progression, extensive caseation with little evidence of repair, and a marked tendency to widespread dissemination of the infection.[12]

Clinically, the seriousness of primary tuberculosis in infancy is reflected by the high mortality rate and morbidity rate in this age group. Based on an extensive study carried out in Baltimore, Maryland, Brailey[13] reported that in white children infected under one year of age the initial x-ray examination showed extensive lesions in the lung parenchyma in 45.5 per cent of cases and large tracheobronchial lymph nodes in about 21.8 per cent of cases. Follow-up studies indicated that large parenchymal lesions carried a high mortality rate. Thus cases diagnosed under 3 years of age had a mortality rate of 20.9 per cent in the white and 35.8 per cent in the Negro within a ten-year period.

According to Lincoln,[1] primary pulmonary tuberculosis diagnosed before the age of 6 months carried a mortality rate of over 50 per cent. Cases diagnosed between 1 and 2 years of age had a mortality rate of 28 per cent.

Available figures of the United States Registration Area for 1940 indicated the mortality rate of tuberculosis in infants under one year of age is about forty times higher than in children from 1 to 4, and about 273 times higher than in the age groups of 5 to 9.[14]

II. ISONIAZID, A VERY POTENT ANTITUBERCULOSIS DRUG

Since the advent of isoniazid in 1952, its effectiveness for tuberculosis has been thoroughly tested in experimental animals. Today there is no doubt that isoniazid is a very potent antituberculosis drug.

Among the animal experiments, the study on rhesus monkeys by Schmidt is of special importance to pediatricians. Monkeys are highly susceptible to tuberculosis. Primary tuberculosis in these primates usually results in extensive caseation and widespread dissemination of the disease in the body. Most of them die within a few months following the acquiring of tuberculin sensitivity. This malignant

course of primary tuberculosis is similar to that which is often seen in the human infant. For this reason, the result of isoniazid therapy of tuberculosis in monkeys is of great pediatric interest.

The large-scale controlled experiment designed by Schmidt[15] to study the curative and the preventive effects of isoniazid on simian tuberculosis was made on several hundred monkeys. The following summary statements made by Schmidt are particularly worth noting:

1. "When administered in daily doses of 20 mg. per kg., isoniazid effectively checks development of established pulmonary tuberculosis. This conclusion is supported solidly by roentgenological and gross necropsy findings, by histopathological data, and by the survival and return to good health of monkeys which appeared to have overwhelming pulmonary disease at the beginning of treatment."
2. "There is a strong suggestion that the above treatment cures the established disease in a high proportion of cases, since homogenates of 'previously infected' tissue from treated monkeys fail to produce tuberculosis in guinea pigs and give negative results on attempted culture in suitable media."
3. "When administered at doses which control the established disease, isoniazid prevents dissemination of tuberculosis to clean (uninfected) monkeys in intimate contact with infected animals."

The results of this experiment bring up two important points in tuberculosis control which deserve thorough studies in the human being; namely, the prevention of primary tuberculosis in children intimately exposed to the disease, and the isoniazid therapy of children with primary tuberculosis. Further discussion of these points will be brought up in Part III of this paper.

The observation made in mice by Deuschle and his associates[16] showed comparative results in the use of isoniazid alone as compared with streptomycin and PAS combined. By means of a precise quantitative technique for enumeration of tubercle bacilli within tissues, it was shown that populations of tubercle bacilli within the lungs or the spleen are suppressed to a much greater extent by the administration of isoniazid than by either streptomycin alone or streptomycin and PAS administered together. The following experimental studies may help to explain the superior therapeutic effect of isoniazid over streptomycin and PAS.

Penetration of Caseous Masses. One of the main difficulties in the treatment of tuberculosis has been the inability of available drugs to penetrate caseous masses. These necrotic residuals which harbor viable tubercle bacilli present great therapeutic problems because their presence not only unduly prolongs the course of the disease, but also is a frequent cause of relapse.

That isoniazid is capable of diffusing into caseous masses was demonstrated in the guinea pig and the human being by the use of C^{14}-labeled isoniazid. With this technique the concentration of this drug can be measured accurately in each tissue by its radioactivity. It was found that isoniazid diffused freely into the body tissues, and that therapeutic concentration of the drug was present in the caseous masses within two hours following a single therapeutic dose.[17]

The penetration of isoniazid into the caseous masses was also studied

by means of inserting caseous material into the subcutaneous tissue of guinea pigs. The fate of the caseous material was observed fifty days later. It was noted that in the control pigs the remains of the caseous material was surrounded by a connective tissue capsule, while in the pigs receiving isoniazid there was no trace of either caseous material or fibrous capsule.[18]

Penetration of Macrophages. It is well known that a significant population of tubercle bacilli is located intracellularly in the macrophages of the body. These bacilli are protected, to a large extent, from such drugs as streptomycin which penetrates poorly into the cells.[19] For inhibition of the growths of intracellular tubercle bacilli, a streptomycin concentration of 25 micrograms per milliliter is required. However, such a high concentration cannot be sustained in the human body fluids without serious toxic effects.

On the other hand, isoniazid penetrates the cells freely[20, 21] and it has been demonstrated that intracellular bacilli were killed in a concentration of 1.0 microgram per milliliter. Such drug level can be safely achieved and sustained in the human body fluids. Studies of the survival rate of tubercle bacilli in isolated mammalian macrophages showed that cultures treated with isoniazid become sterile within eleven days, and such bactericidal effects could be much enhanced by the combined use of isoniazid with streptomycin.[22]

The ultimate test of a drug is its effect on the disease as it is found in the human body. In the past four years isoniazid has been used extensively in the treatment of various clinical forms of tuberculosis. To date, accumulated clinical data have proved beyond doubt that isoniazid is a potent drug for human tuberculosis. Some of the following studies show what isoniazid alone can achieve. However, in clinical practice isoniazid is usually administered together with PAS and/or streptomycin for the purpose of enhancing its therapeutic effect.

Miliary tuberculosis is a critical test for antituberculosis agents, because when untreated this disease is almost always fatal. Isoniazid is standing the test. Clark and his associates[23] treated a series of patients, using isoniazid alone. Uniformly satisfactory results were obtained. There were prompt clinical and x-ray improvements. No relapse of disease has been observed during or after appropriate treatment with isoniazid therapy.

Similar success was obtained in the treatment of miliary tuberculosis in children. Lincoln[24] reported excellent results using isoniazid in combination with promizole, even when no streptomycin was added to the treatment regime.

Tuberculous meningitis was a uniformly fatal disease until the antibiotic era. Since the advent of streptomycin and PAS, many lives have been saved; however, among the survivors many were seriously crippled because of permanent brain damage. In this country the result obtained by Lincoln and her associates has been better than many others because of early diagnosis and treatment of this disease. Lincoln[24] reported a mortality rate of 37 per cent in cases treated with streptomycin combined with sulfone between 1947 and 1951. Since 1952, isoniazid was added to the treatment regimen. The result was a remarkable improvement. The death

rate dropped to 12 per cent, and the incidence of crippling was also reduced among the survivors.

In Canada, Boyd[25] reported a remarkable improvement in the results for tuberculous meningitis in children with the addition of isoniazid to the therapy regimen.

Tuberculous meningitis is the most frequent cause of death and brain damage in tuberculous children. This serious complication may happen despite streptomycin therapy. An outstanding attribute of isoniazid is its effectiveness in preventing tuberculous meningitis, for no case of tuberculous meningitis has been reported in patients receiving isoniazid.[16, 24, 29] This is true even in miliary tuberculosis in which the incidence of meningitis has been reported as high as 70 per cent.[30] In this respect isoniazid is distinctly superior to streptomycin.

Clark and co-workers[23] and Lincoln[24] reported instances in which tubercle bacilli were found in the spinal fluid in patients receiving isoniazid, but, remarkably enough, meningitis failed to materialize in these cases. The patients did not develop clinical manifestations or the spinal fluid changes of tuberculous meningitis.

Despite the marked reduction of the mortality rate of tuberculous meningitis, this disease remains a serious condition, because good end results can be expected only in patients treated early. Too often the diagnosis is made so late that by the time treatment is started permanent brain damage has already taken place. Although antimicrobial therapy can cure tuberculous meningitis, the damaged brain cannot be restored and, as a result, the child becomes crippled or mentally defective. For this reason it is important to prevent tuberculous meningitis by the use of isoniazid.

Chronic Pulmonary Tuberculosis in Adults. The comparative effectiveness of isoniazid, streptomycin, and PAS in various combinations for chronic pulmonary tuberculosis has been studied in a large number of patients under the auspices of the U. S. Public Health Service. The report on a forty-week observation on 583 patients showed isoniazid alone was as effective as streptomycin in combination with PAS in bringing about clinical and x-ray improvement and sputum conversion.[26, 27]

III. CLINICAL USE OF ISONIAZID IN CHILDREN

The accepted dosage of isoniazid for adults is 4 to 5 mg. per kilogram, which is approximately 300 mg. per day. The optimum dosage for children is yet to be learned by the pediatrician. Among the rules devised to relate adult doses to children, the calculation of dosage on the basis of surface area appears more appropriate than a calculation on body weight or age. However, this rule does not apply to all drugs. For some drugs a child requires only a small fraction of the adult dose, for others a child may need almost an adult dose, as is particularly true with many antibiotics. For this reason it is often necessary to determine the dosage of a drug by carefully conducted clinical trials.

So far the dosage of isoniazid for children has been generally calculated on the basis of body weight. At a daily dose of 4 to 5 mg. per kilogram a child receives only a fraction of the adult dose. This dosage would appear insufficient on the basis of surface area. For the treatment of meningeal

and miliary tuberculosis, a daily dose of 8 to 10 mg. per kilogram has been generally used with good results. Experience with tuberculosis in monkeys, as reported by Schmidt,[15] showed that a dosage of 5 mg. per kilogram was inadequate to control the infection, whereas excellent therapeutic results could be achieved with a dosage of 20 mg. per kilogram. More studies are needed to determine the adequate dosage of isoniazid for children in order to obtain the full benefit of this drug.

The currently accepted principles and practices of antimicrobial therapy of tuberculosis emphasize the combined use of two or more drugs given continuously for at least a year even in minimal cases.[31] The purpose of multiple drug therapy is twofold; namely, to enhance the drug effect and to delay the emergence of drug-resistant tubercle bacilli. Isoniazid is the basic drug for all drug regimens. Streptomycin and/or PAS are administered as adjuvants. Of the two, PAS appears more effective than streptomycin in delaying the emergence of isoniazid-resistant tubercle bacilli.[28] Triple drug therapy, that is, isoniazid plus streptomycin and PAS, is reserved for severe cases such as tuberculous meningitis, miliary tuberculosis, and acute caseous pneumonia, in which instances immediate maximum drug effect is desired.

The dosage of streptomycin for children is 30 to 40 mg. per kilogram per day given twice weekly. Meningeal and miliary tuberculosis require a daily dose of 100 mg. per kilogram, with a maximum of 1 Gm. To avoid toxicity this high dosage is seldom maintained longer than four to six weeks.

The adult dose of PAS in the form of PAS-sodium is 15 Gm. daily, which is approximately 200 mg. per kilogram of body weight. At the Houston Tuberculosis Clinic we found the children tolerate this dosage of 200 mg. per kilogram very well. Higher doses are liable to cause nausea, vomiting, and diarrhea, which can be a serious problem, especially in infants.

Toxicity of Isoniazid.—Isoniazid is the least toxic of the antituberculosis drugs so far discovered. When used in the therapeutic dose of 5 mg. per kilogram per day in adults, it is practically nontoxic.[32] At higher dosage, toxic symptoms may appear. The most commonly observed has been peripheral neuritis. Oestreicher and his associates[33] reported eight cases of peripheral neuritis among 500 adult patients who received a daily dose of 4 to 8 mg. per kilogram. Seven of the eight had histories of alcoholism. On discontinuation of isoniazid and administration of pyridoxine, six patients showed marked improvement.

Patients with a history of convulsive disorders are prone to develop convulsions under isoniazid therapy; therefore, isoniazid should be given with great caution and with adequate anticonvulsant medication. Patients who show impairment of renal functions may accumulate the drug to toxic concentration in the body. It is important to reduce the dosage according to the plasma level of the drug.

Other side effects, such as drug fever, dermatitis, abnormal bleeding, leukopenia, albuminuria, and cylinduria, have been reported in a few instances. However, it was impossible to be certain that these reactions were all due to isoniazid. It would seem wise

for clinicians prescribing the drug to watch for any of these reactions.[24]

During the past two years 150 children have been given isoniazid therapy at the Houston Children's Tuberculosis Hospital and Clinics at a daily dose of 3 to 5 mg. per killogram. In addition, eighteen hospital patients were given a daily dose of 10 mg. per kilogram. No toxic symptoms or signs attributable to the drug were noted in any case.

The Problem of Isoniazid-Resistant Tubercle Bacilli.—Isoniazid-resistant tubercle bacilli have been isolated from patients receiving isoniazid therapy. The clinical significance of isoniazid resistance is not clear at this time. The problem is much more complicated than in the case of streptomycin resistance which usually means loss of drug effect. In contrast, isoniazid resistance is often associated with a loss of pathogenicity of the tubercle bacilli in varying degrees. Recent work of Oestreicher and his associates[29] demonstrated a deficiency of endogenous catalase activity in the isoniazid-resistant mutants and found the degree of attenuation of the bacilli is related to the degree of deficiency of catalase activity. Thus catalase-negative, isoniazid-resistant mutants are highly attenuated for guinea pigs; whereas, catalase-positive mutants exhibit various degrees of attenuation.

Much work has been done to test the pathogenicity of the isoniazid-resistant mutants in experimental animals. The reports have been conflicting. Many strains proved to be nonpathogenic to the guinea pig. Others were found to be capable of producing tuberculous lesions in mice.

In the treatment of tuberculosis, drug resistance does not appear to interfere with the success of isoniazid therapy in many instances. The high percentage of cure achieved in the tuberculous monkeys[15] did not suggest that drug resistance was a hindrance to therapy. The good result of treating miliary tuberculosis with isoniazid alone showed a well-sustained therapeutic effect during a long course of therapy.[23] Likewise, the successful control of noncavitary pulmonary tuberculosis as reported by USPHS[26, 27] also indicated that isoniazid resistance did not significantly curtail the period of therapeutic effectiveness of isoniazid.

The problem of isoniazid resistance concerns mainly the advanced cases of chronic cavitary disease. The resistant tubercle bacilli have been encountered most frequently in such cases, and the development of drug resistance in these instances may be associated with progression of the disease.

It must be admitted that our present-day knowledge of isoniazid resistance is imperfect. Therefore, in clinical practice the consensus is to use isoniazid in conjunction with PAS in an attempt to delay the emergence of isoniazid-resistant tubercle bacilli.

IV. ANTIMICROBIAL THERAPY OF PRIMARY TUBERCULOSIS. A NEW APPROACH TO TUBERCULOSIS CONTROL

Changing Concepts of Tuberculosis Control.—With the improvement of diagnostic methods and the discovery of new effective therapies, there has been a constant change in concepts of tuberculosis control. Fifty years ago tuberculosis control was limited to the care of the sick and the dying, because the disease could not be diagnosed until a person became ill and developed

obvious symptoms and signs of "consumption."

Since the improvement of x-ray technique and the development of photofluorographic methods, it has been demonstrated that tuberculosis can be detected in the lungs long before a person falls ill from the disease. These asymptomatic cases will go unrecognized unless an active search is made to find them among apparently healthy people. Furthermore, these unrecognized cases constitute the main reservoir of tuberculous infection in a community and serve to spread the infection to family and social contacts; thereby perpetuating a continuous stream of new cases of tuberculosis. The discovery of important facts such as these has changed the concepts of tuberculosis control. It became clear that while it is important to isolate and care for the sick and the dying, it is of greater importance to find tuberculosis in people before they become clinically ill with the disease. It is for this reason that much of the effort of tuberculosis control during the past three decades has been directed to case finding by x-ray surveys.

In the past ten years the discovery of potent antituberculosis drugs and the rapid development of thoracic surgery have made spectacular advances in the treatment of tuberculosis. As a result, a dramatic decline in deaths from tuberculosis has taken place. Such achievement certainly can be viewed with pride and satisfaction. Yet, tuberculosis is far from being conquered, for the falling death rate does not necessarily mean falling case rate. Actually, tuberculosis has been converted from a killing disease to a chronic disease; therefore, more people are probably living with tuberculosis today than before. Among the survivors of tuberculosis victims, many are actually or potentially contagious, remaining as sources of infection in the community. As was recently pointed out by James E. Perkins,[36] the Managing Director of the National Tuberculosis Association, new cases of active tuberculosis are continuing to occur in the United States at the rate of 100,000 each year. While we have been occupied with the job of mending the damage done by tuberculosis, insufficient effort has been directed toward the prevention of the disease.

At the beginning of this review it was pointed out that primary tuberculosis is the fountainhead of tuberculous diseases. Every individual with primary tuberculosis, as evidenced by a positive tuberculin reaction, is a potential case of active tuberculosis. These infected individuals constitute an enormous human reservoir of tubercle bacilli from which all cases of clinical tuberculosis evolve. These facts must be borne in mind in planning an effective tuberculosis control program. In the past the main concern in tuberculosis control has been the finding and the healing of gross lesions. It now begins to come to light that unless primary tuberculosis is included in the over-all control program, many new cases with gross lesions will continue to appear. To neglect primary tuberculosis is like leaving a break in a dike; as long as the break persists the flood is destined to continue.

Last year when the National Tuberculosis Association observed its golden anniversary, this "break in dike" was promptly recognized as an important defect of tuberculosis control in the past. Dubos[37] called attention to "the enormous and unchartered (human)

reservoir of tubercle bacilli'' and pointed out how latent infections can be provoked to active tuberculous diseases. Myers[38] stated, ''In the past little effort has been made to attack the vast armies of tubercle bacilli to prevent their destructiveness. Most work has consisted of following far behind these armies and trying to repair the damage they have done. The time has arrived when the major attack must be made upon the tubercle bacilli itself rather than waiting until infected persons have developed implantations which have resulted in symptoms, are liberating tubercle bacilli, or casting visible roentgenographic shadows.''

The present concept of tuberculosis control emphasizes the prevention and the control of primary tuberculosis. For this reason, tuberculin testing, which has long been ignored and disregarded, is being revived with vigor by the National Tuberculosis Association in the United States. The Federal Tuberculosis Control Program now recognizes three specific goals; namely, the prevention of the spread of infection, the prevention of illness among those infected, and the prevention of death from tuberculosis. For the control of tuberculosis emphasis is laid not only on clinically manifest tuberculosis but on latent primary tuberculosis as well. Since the discovery of isoniazid, a new method has become available for preventing illness from primary tuberculosis. This new approach of tuberculosis control will be the subject of intensive investigation in the coming years.

Thus the concepts of tuberculosis control have been changed from caring for the sick and the dying to the search for unrecognized cases among the apparently healthy. Attention is now being drawn to primary tuberculosis, which is regarded by many as the root of the tuberculosis problem.

The Prevention of Illness by Isoniazid Therapy of Primary Tuberculosis.—Isoniazid is the first drug which makes possible chemotherapy of primary tuberculosis. Since most children with primary tuberculosis do not require hospitalization, the only feasible therapy would necessarily be one which can be easily and safely administered at home. Isoniazid is the first potent antituberculosis drug which meets these requirements. It can be taken by mouth; therefore, it requires no injections. As tablets or as an elixir it is acceptable to the children because of the absence of unpleasant odor or taste. For this reason regularity and continuity of administration can be expected. Toxicity is seldom encountered when standard therapeutic dosage is used. Finally, isoniazid is so inexpensive that a whole year's supply for an infant would cost fifty cents or less. When given with PAS, the total yearly cost would amount to about one dollar.

For prevention of tuberculous diseases, there are several reasons why it is important to administer isoniazid therapy in the early stage of primary tuberculosis.

1. *Isoniazid Most Effective on Actively Multiplying Tubercle Bacilli.* During the first year of infection, primary tuberculosis is in its active stage. After this time it gradually submerges into an inactive state. As a result, the tubercle bacilli in the lesions enter into a dormant state for which isoniazid has virtually no bactericidal effect.[35] In order to capitalize on the drug action of isoniazid it

must be used during the early stage of the infection.

2. *To Prevent Postprimary Complications.* The primary tuberculosis is particularly active during the first few months when the tubercle bacilli multiply rapidly. The great majority of serious complications such as meningeal and miliary tuberculosis and caseous pneumonia occur at this time. To prevent these serious complications, isoniazid therapy must be started as early as possible.

3. *To Minimize the Potentiality of Future Reactivation.* Large caseous masses are the usual cause of future reactivation of primary tuberculosis. To minimize the potentiality of future reactivation, isoniazid can be used to the best advantage during the early stage of the infection by preventing the formation of extensive caseating lesions.

4. *Hematogenous Seedings a Dangerous Component of Primary Infection.* It is important to realize that the hematogenous dissemination of tubercle bacilli which constantly occurs during the early phase of primary infection is a very dangerous component of primary tuberculosis. This is because the tubercle bacilli seeded in various tissues of the body are directly responsible for many serious tuberculous diseases later in life. These potentially dangerous tuberculous foci which are usually asymptomatic can seldom be detected even by the most careful clinical examinations. Therefore, antimicrobial therapy offers the only treatment. Isoniazid has proved to be effective in controlling the most severe form of hematogenous spread; namely, miliary tuberculosis. There is good reason to believe that it would offer the best answer to hematogenous seedings.

The antimicrobial therapy of primary tuberculosis has recently been strongly advocated by investigators of tuberculosis as a new approach to tuberculosis control. H. Stuart Willis,[36] President of the American Trudeau Society, calls attention to "the large army of children who react to tuberculin" because these children are now recognized as potential tuberculous patients of tomorrow. James J. Waring[39] says, "Now that we have potent, inexpensive, and easily taken antibiotics against the tubercle bacillus, every effort should be made to identify the moment of infection, the time of conversion of the tuberculin test, so that treatment may be started." As for tuberculosis in children, he expressed that all cases of early "uncomplicated" as well as "progressive" tuberculosis in children should receive the benfits of early chemotherapy. J. Arthur Myers[38] stated in a recent editorial, "If drugs are to be effective in curing tuberculosis in the sense of destroying all tubercle bacilli in the human body, they must be administered soon after invasion occurs. Present chemotherapy administered as soon as possible after the invasion occurs, as recommended by Waring, should be given a thorough trial. If this succeeds, as it may well do, it will be possible to banish illness from tuberculosis."

The present status of antimicrobial therapy of tuberculosis in children has recently been summarized by the Committee on Chemotherapy and Antibiotics of the American College of Chest Physicians as follows:[31] "During

the past two years there has been an increasing tendency to treat active tuberculosis in children with antimicrobials, especially isoniazid. The complications such as miliary and meningeal tuberculosis, which sometime occur in active primary disease, have sharply declined since the advent and use of isoniazid. Whether all cases of active primary tuberculosis should receive antimicrobial therapy has not yet been determined, but adherents to this view are increasing."

The studies of Schmidt[15] on tuberculosis in monkeys have brought forth convincing pathologic and bacteriologic evidences that isoniazid therapy can bring about cure of primary tuberculosis in a high percentage of cases, even in its malignant form as seen in the monkey. The results of this study should stimulate and encourage the use of isoniazid for primary tuberculosis and its complications in children.

Pediatricians' Responsibilities in Tuberculosis Control.—The basic concept of pediatrics is one of prevention—the prevention of deviation from normal. Throughout the ages one of the prime responsibilities of the pediatrician has been the prevention of infectious diseases. Since the opening of the antibiotic era, many serious infectious diseases and their grave consequences have become preventable by the use of antimicrobial drugs. Type A streptococcus infection is an example. Infection by this organism was frequently fatal, especially in young infants. Septicemia, mastoiditis, and lymphadenitis were the usual early complications. Those who survived the acute stage of the disease not infrequently became the victims of rheumatic fever and glomerulonephritis weeks or months later. Today with the use of penicillin this infection not only can be cured, but also becomes preventable.[40, 41] An adequate course of therapy given during the acute stage will eliminate the streptococci from the throat, and cut down to the minimum the early as well as the late sequelae of this infection.

Primary tuberculosis and its early and late sequelae have been described in Part I of this paper. Now since potent antituberculosis drugs are available (Part II), it is the responsibility of the pediatrician to give children the benefits of these drugs for the prevention of the grave consequences of primary tuberculosis. Since antimicrobial therapy is most effective when applied in the early stage of primary tuberculosis, tuberculin testing has become a tremendously important diagnostic procedure, because it is the single most effective means of detecting primary tuberculosis in its early stage. It is important to realize that most children with primary tuberculosis look perfectly well, and in the great majority of instances their chest x-rays do not reveal gross lesions. A positive tuberculin reaction often gives the only clue of the presence of tuberculous infection. For this reason, it is important to make tuberculin testing a routine pediatric procedure for every child, no matter how well he may look. For those who show a negative reaction to the initial test, follow-up testing at regular intervals is necessary to detect the time of conversion of tuberculin reaction which marks the onset of primary infection. Periodic tuberculin testing is particularly

important for children from tuberculosis homes, and in communities where the incidence of tuberculosis is high.

A positive tuberculin reaction in an infant always means active tuberculosis, because the child has not lived long enough to allow the infection to heal. In older children a recently acquired tuberculin sensitivity is a certain indication of a fresh primary infection. These children should be given the benefits of antimicrobial therapy for reasons stated before. Aside from infants and the tuberculin converters, there are large numbers of children who show positive tuberculin reaction to their first tests and in whom the duration of infection is unknown. These cases present a challenge to the attending doctor. It requires a complete clinical examination to assess the activity of the tuberculous infection in such cases. In some instances the activity of the infection is evidenced by the demonstration of tubercle bacilli in the gastric contents, in others by enlarged peripheral lymph nodes which prove tuberculous by biopsy. Enlarged hilar lymph nodes are often hidden by the mediastinal shadows in an anteroposterior chest film and lateral views are often necessary.

If initial examinations do not disclose signs of active disease, the child should be examined periodically so that if active disease occurs it can be detected in its early stage. The follow-up examinations are particularly important during and following adolescence when latent tuberculous infections are likely to break down, producing active tuberculous diseases.

When a child with primary tuberculosis is found, the pediatrician must recognize the public health aspects of the problem. Since practically all the children get their infection from their adult associates, a positive tuberculin reaction in a child is an alarm signal which indicates the presence of a contagious case of tuberculosis in the immediate environment of the child. In the case of infants, the source of infection is almost always found in the household. Usually there is no difficulty in finding the tuberculous member by x-ray examination. Every effort should be made to isolate or remove the tuberculous adult before more children become infected.

Large-Scale Clinical Investigation Will Promote Progress and Set Standard of Antimicrobial Therapy of Primary Tuberculosis.—Since the advent of antimicrobial therapy of tuberculosis, many clinical problems found their answers in large scale cooperative investigations such as those conducted by the Veterans Administration, the Public Health Service of the United States, and the Medical Research Council of Great Britain. The knowledge gained from these studies has served as a guide to the clinicians in regard to the choice of drugs, drug combinations, the dosage requirements, the necessary duration of therapy, and other therapeutic problems. Through cooperative efforts large numbers of patients can be treated and studied. In this way the efficacy of a given therapeutic regime can be properly evaluated in a much shorter period of time than would be possible with any individual investigator or clinic. Furthermore, by having many clinicians of different hospitals and clinics participating in a common research project, it would not only stimulate interest, but also

facilitate dissemination of information on the treatment of tuberculosis.

Isoniazid therapy of primary tuberculosis is a recent development. Its therapeutic potentialities are yet to be explored. Problems such as indications for therapy in regard to the age of the child and the duration of primary infection, optimum dosage and duration of therapy, necessity of PAS as an adjunct, and many others, can find answers only by clinical trials. It is important that clinicians and public health officers be informed of this newly opened way for tuberculosis control so that large numbers of children can be treated and studied at clinics and institutions as well as in private offices.

In the United States a large-scale cooperative investigation on the effect of isoniazid in preventing tuberculous diseases was started about a year ago under the joined auspices of the Public Health Service and the National Tuberculosis Association. Currently, thirty-two children's clinics are participating in this nationwide project. In France, clinical tests on a large number of young children are also underway.

Infants born to households of open tuberculosis are almost always infected if the contact cannot be broken. Chemoprophylaxis is highly desirable under such circumstances. The use of isoniazid for prevention of primary tuberculosis deserves investigation.

It is important to point out that the severity of primary tuberculosis varies considerably in different parts of the world according to the local epidemiologic situation of tuberculosis. For proper evaluation of isoniazid therapy it is necessary to include in the test a sufficiently large number of severe cases of primary tuberculosis. There are many countries in the world today where tuberculosis is still very prevalent. In these countries primary tuberculosis is extremely common in children. In some areas, as many as 50 per cent are infected before reaching school age and the infection is usually so severe that many become sick and die of tuberculosis. Prevention of illness by drug therapy is a crying need of these infected children. Clinicians in such places have an excellent opportunity of making a clinical study of great practical importance. Because of the prevalence and the severity of primary tuberculosis, these places make good testing grounds for isoniazid therapy. Since the great majority of tuberculous diseases during childhood develop within a year of the primary infection, the protective effect of isoniazid for the infected children can be evaluated within a year or two. Follow-up studies of the treated and the untreated cases would contribute much to the knowledge of primary tuberculosis and its drug therapy—a knowledge which is badly needed for tuberculosis control all over the world today.

SUMMARY

Primary tuberculosis is the fountainhead of tuberculous diseases. When acquired during childhood, it may develop into serious tuberculous diseases within a short period of time, or it may remain latent during childhood only to become reactivated in adult life, giving rise to such condition as chronic pulmonary tuberculosis. Until recently, little could be done to control the natural conse-

quences of primary tuberculosis. As a result, large numbers of infected children and adults continue to fall ill with tuberculosis.

The discovery of isoniazid has opened a new hope. Animal experiments have brought forth convincing evidences that isoniazid is effective in controlling primary tuberculosis, even in its progressive form. Clinical experiences strongly indicate that serious tuberculous diseases can be prevented in infected children by the early institution of isoniazid therapy. Since its use three years ago, there has been a sharp decline in the incidence of tuberculous meningitis and miliary tuberculosis in children.

Now that primary tuberculosis can be treated, it is more than ever a regret that a child be allowed to develop serious tuberculous diseases. Pediatricians and public health officers must assume their new responsibility of recognizing primary tuberculosis and make available to infected children the benefit of modern drug therapy. There is no other means which can detect primary tuberculosis as early and as accurately as a simple tuberculin test. For this reason, tuberculin testing must be made a routine pediatric procedure in well-baby clinics, nurseries, and schools, as well as in children's clinics and in private practice.

One of the greatest pediatric triumphs in the United States is the conquer of congenital syphilis in the current generation. This was accomplished by public education, universal serologic tests and vigorous drug therapy of the syphilitic pregnant mothers. Today the principle of tuberculosis control should be universal tuberculin testing and vigorous drug therapy of tuberculosis in children and adults. There is yet much to be learned about primary tuberculosis and isoniazid therapy. Most likely, newer and better drugs will be discovered. From now on a large share of the responsibility of tuberculosis control will fall on the shoulders of pediatricians. Primary tuberculosis can no longer be neglected.

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Psychologic Aspects of Pediatrics

WHY JOHNNY CAN'T READ: FACT OR FALLACY?

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RUDOLPH FLESCH'S book *Why Johnny Can't Read* has focused public attention on important issues of American education. This interest is in itself healthy, and, to the extent that Flesch has helped to stimulate public concern with our teaching methods, he has rendered a service. Unfortunately, however, the book has had an unnecessarily misleading influence on the attitudes of the lay public. Far from being an objective, illuminating study of reading education, *Why Johnny Can't Read* is a partisan, argumentative discussion which generates a great deal more heat than it throws light on the subject.

METHODS OF TEACHING READING

The issues involved cannot be fully understood without an appreciation of the background of the problem. Until about 1930, the so-called "phonic" system was used almost exclusively in American elementary schools. By this system the child is taught to associate the proper sound with the printed letter, and later to "build" groups of sounds into words. During the 1930's emphasis shifted from the "phonics" system to the so-called "word" method (also known as the "look-and-say" technique). Basically this system teaches the child to associate the printed word directly with its meaning. The point which Flesch tries to prove in his book is that the phonics system, which is still the chief teaching method in Europe, is superior to the word method.

No doubt much of the furor created by Flesch's book was due not so much to his advocating the long-since-abandoned phonics method as to his contention that the look-and-say method actually delays and impairs the development of reading ability. It must have taken a great deal of courage for Flesch to set himself up in opposition to the almost unanimous opinion of American Education experts. It is unfortunate that he found it necessary to state his arguments in a manner which suggested that the weight of reason and of research results was entirely on his side. It is even more regrettable that in his zeal to make his points, Flesch is guilty of a great deal of peculiar reasoning and distortion of fact. Clearly, the proper education of children is too important an issue to be argued on the level of old-time ward politics. Only a full and fair statement of the issues involved, without bias and without rancor, can lead to an intelli-

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gent solution. It is tragic that Dr. Flesch, who has caught the public's imagination so successfully, should have wasted his fine opportunity to clarify public understanding.

Perhaps one of the most misleading aspects of Flesch's presentation is the fact that nowhere in his book does one find a really concise, adequate statement of the two methods.

When the phonics technique is taught in the classroom, "Johnny" first learns the sounds of the letters. For example, the teacher may point to the letter "s" and explain that it makes a sound like a snake. The children then hiss in imitation of the teacher. Johnny continues to learn in this way until he has mastered all of the sounds. At the same time he learns to blend various combinations of sounds such as *bl, cr, tu, ba,* and so forth. Finally he learns to analyze and to build words from these letter sounds. In this way new words are added to his reading vocabulary.

When taught by the "word" method, Johnny first learns whole phrases and sentences. The teacher may draw a picture on the blackboard and under it write the words "This is a boy." Under another picture may be written, "This is a girl," and so on. Johnny soon recognizes "*This is a*" to be a unit, and he can then change the sentence as he learns new words.

After three or four months, Johnny will have a "sight vocabulary"; that is, he will now recognize many words at a glance. At this point, *but not until this point,* the word method takes advantage of phonetic analysis. Words that are basically phonetic (i.e., can be sounded out) are stressed, but the words that are not basically phonetic remain sight words. In this way Johnny recognizes that all words *cannot* be sounded.

The English language abounds with nonphonetic words, and this is one of the biggest stumbling blocks for the phonics method. Although Flesch tries to minimize this difficulty, objective studies have repeatedly shown that the letter combinations most frequently used in primers have an average of between three and four sounds each.[1, 2] For example, the combination *at,* which is commonly taught in the first grade, occurs in at least eleven different pronunciations in primer readers. Having learned to pronounce f*at,* r*at,* and h*at,* we can hardly blame the child for stumbling and becoming confused when he later runs into wh*at,* n*at*ion, or m*at*erial.

For better or worse, the English language is full of arbitrary sound combinations that make no phonetic sense. The teaching system must be geared to the language as the child will have to read it. This is the fundamental reason why American educators have abandoned exclusive reliance on phonics in favor of a more comprehensive approach based on the word method. Here four techniques are simultaneously brought into play: (1) acquisition of a sight vocabulary by rote, (2) phonic analysis *where it can be applied,* (3) analysis of words into elements (such as common, easily memorized prefixes and suffixes), and (4) the use of context clues (grasping the meaning of the word by inference from the rest of the sentence). When phonics is made a part of this larger program, it is referred to as "incidental" phonics.

Thus modern methods utilize every available device, *including phonics,* to teach the child to read. The phonics method employs o n l y *one* device,

which is not adequate for all the problems of reading. Yet, somehow, Flesch contrives to claim that the present teaching method deprives the child of an essential element of his education!

REVIEW OF LITERATURE

Flesch apparently bases his argument on the studies which he reviews in his book. He says in his introduction:

". . . Whenever the results of phonics and of the word method were compared by tests and experiments, phonics came out on top. . . . Let me repeat that statement and amplify it: In every single research study ever made phonics was shown to be superior to the word method; conversely, there is not a single research study that shows the word method superior to phonics."

Now let us consider some of the "true facts" which Flesch quotes. The first study that he refers to is one by C. W. Valentine[3] published in 1913. Flesch explains a little of Valentine's procedure and then states his own interpretation of the results: "Those who had learned the alphabet did 200 per cent better." He quotes Valentine as saying that the results of the experiment added up to a "striking victory for the phonic method."

In the actual study, Valentine selected children who had already been taught by the phonics method. To half of these students he presented Greek words, also taught by the phonics method. To the other half he presented the same Greek words but this time used the "word" method. Since the phonics group had already learned to read English by the phonics technique, they were naturally better prepared to utilize this technique when presented with the Greek words. This placed the second group at a disadvantage since they were taught English by one technique and Greek by another. They were forced to learn twice as much, (1) a series of unknown Greek words and, (2) a new technique for learning them. Thus the "cards were stacked" in favor of the phonics group. Most modern investigators avoid such glaring errors as these.

Valentine, in the course of his experiment, realized that he was presenting more Greek words to the word method group than to the phonics group. To correct this, he cut down the amount of material presented to the word method group. Valentine said, after changing his procedure, "The change in method obviously caused a considerable change in results." It certainly did. The word method group, despite their previous training in phonics, remembered 240 per cent *more* of the words than did the phonics group.

Valentine erred further by distinguishing between bright students and dull ones through the use of teachers' ratings of reading ability. Since all of these children had already completed four years of phonics training, the ones who had learned to read well by this technique were called "bright," but those children who had not thrived under phonics were called "dull." By comparing the "dull" group with the "bright" group Valentine concluded: "There seems to be some evidence that for very dull children the 'look-and-say' method is more efficient."

But this is circular reasoning. Were the "bright" children *really* brighter, or simply better adapted to the phonics method? We must con-

clude that Valentine's work, Flesch notwithstanding, sheds very little light on the problem.

The second study that Flesch reports is by Lillian Currier and Olive C. Duguid[4] written in 1916. Flesch sums up their conclusions in this way:

"She had no statistics to offer but reported that the 'non-phonic' children read with more expression and interest, but the 'phonic' children were more careful and more accurate in reading the words that were on the page."

This implies that Currier and Duguid found phonics more effective, while the word method was merely more pleasant. Actually this was not their opinion at all. Here is a direct quotation:

"The phonic classes so concentrated upon letter sounds that the attention was diverted from the sense of the paragraph to word pronunciation. This brought about lack of interest and fatigue and destroyed the pleasure which the story should yield. The reading was generally less smooth, slower, and the idea confused.

"The classes having no phonics were found to enjoy reading for the sake of study. From the story they got the sense-content. They were less careful and less correct than the phonic classes in regard to word pronunciation. Keeping the sense in mind, they often substituted words from their own vocabulary for difficult or unfamiliar words in the text. They read more swiftly and with more expression. Fatigue was reduced, because curiosity in the story held the interest and caused the attention to be focused upon the outcome of the story.

"From time to time stories with which the children were unfamiliar were assigned for them to read silently, entirely unassisted. At a signal books were closed and the pupils were asked to reproduce what they had read. Many of the children of the phonic classes, although very accurate in word pronunciation, were almost helpless when this reproduction was required. Those in the non-phonic classes were, in most cases, able to give clear ideas of the contents."

Clearly, Currier and Daguid have little to offer in favor of phonics. One wonders why Flesch saw fit to omit the major findings of this article from his quotation. To make his argument stronger, perhaps?

Next he mentions an article by W. H. Winch,[5] "Teaching Beginners to Read in England, published in 1925. Flesch says this about Mr. Winch's results:

"There were two groups of children, one taught by the phonic method, the other by the 'look-and-say' (That is, the whole word method.) After two months the children were given four tests. The look-and-say group scored 62.8, the phonic group 79.1. Mr. Winch summarized these results simply: 'The phonic group has scored a complete victory.'"

It is important to note, however, that the study was made on *retarded* children. The studies reported thus far were made on *normal* children and these all favored the word method. Flesch errs in trying to apply results obtained from a small, special group to *all* children. The Winch study simply has no bearing on the problems of teaching *normal* children to read.

The fourth study quoted by Flesch is "The Newark Phonics Experiment" of Sexton and Herron[6] published in 1928. Flesch says:

"Sexton and Herron tested a thousand school children in Newark, New Jersey. . . . They concluded that the

results favored instruction in phonics."

This would probably be news to Sexton and Herron. They clearly state:

"Although the outcome of the experiment tends to favor some phonetic instruction, beginning in the second half of the first year, just what type of phonics should be taught and to what extent are still problems for experimentation."

Note that Sexton and Herron specifically state "beginning in the second half of the first year." This is exactly what the word method does: it brings phonics into play only when the child is ready to profit from it fully.

Here is Flesch's review of the article written by Mosher and Newhall.[7]

"In October 1930 *Journal of Education Psychology* Raymond M. Mosher and Sidney M. Newhall report on 'Phonic vs Look-and-Say Training in Beginning Reading.' Fifty children in New Haven, Connecticut, were taught by the word method and seventy-three children by the phonic method. The two groups were given ten tests. Eight of the ten tests favored phonics."

Flesch's report of this study is not only a clear misrepresentation of the outcome but also shows his misunderstanding of scientific data. Mosher and Newhall state that there were no *statistically significant* differences between the group trained with phonics and the group trained by the word method. The differences in scores between the groups were so small that they probably were due entirely to chance factors, rather than to a real advantage of one method over the other.

Mosher and Newhall gave ten tests. The results in only two of these even approached statistical significance and those *favored the word method group.* Mosher and Newhall concluded that both "individually and collectively no essential difference existed between the groups." Yet Flesch claims that this experiment supports phonics!

The sixth study was one by Helen Braem,[8] Head Teacher at Letchworth Village, a state institution for mental defectives. Flesch reported the results accurately, but he neglected to mention Miss Braem's final conclusion:

"Although the phonetic method may not be the best for normal children, judging from the results of our experiment, it would seem that mentally defective children learn to read much faster by its use than by the Sight Reading Method."

But the techniques used in dealing with a dull child are quite different from those used with normal children. This is another case of unwarranted generalization by Flesch, with omission of crucial points.

The seventh study cited by Flesch is by Garrison and Heard[9] in 1931. Again a phonics group was compared to a nonphonics group. Here is how Flesch quotes the results of their experiment:

"Total result: The phonics group scored 58.5, the other group 55.5. Three points in favor of phonics. *And,* Garrison and Heard report, the phonics group was also considerably better in spelling."

This study differs from the others in that, while the word method group had *no phonics,* the phonics group had *both* the word technique and supple-

mentary phonics. In this case we are comparing instruction with "incidental" phonics to completely nonphonic teaching. Flesch has no sympathy for the use of incidental phonics. He insists that phonics be taught exclusively, without any of the sight method techniques. Thus it seems strange that he would so willingly accept the Garrison and Heard data in which "pure" phonics were not used.

Since the conclusions of Garrison and Heard are extensive, only parts of them will be cited here.

1. "Children with no phonetic training make smoother and better oral readers in the lower grades.

2. "In the teaching of reading it seems probably that much of the phonetic training now given should be deferred till the second and third grades. It appears that work in meaningful exercises which are planned to increase comprehension and to teach discrimination of words is more important than phonetics."

As to spelling, Garrison and Heard found that phonics seem to be helpful only with *new* words. Words that were taught in class were learned equally well whether or not phonics had been taught.

All Flesch chose to report from the Garrison and Heard study were the two scores of 55.5 and 58.5. This difference probably occurred by sheer chance; that is, if the experiment were repeated, the difference might just as easily favor the other side. The figures on which Flesch places so much stress are meaningless, as Garrison and Heard were careful to point out.

Next Flesch quotes a study by Harry L. Tate[10] entitled, "The Influence of Phonics on Silent Reading in Grade I." As in the last study the word method was used for both groups, but in one group phonics were also taught. This is how Flesch reports the study:

"After two months they were given three tests. Two of the tests ('Silent reading' and 'paragraph reading') were tests of guessing rather than reading, and the word method children scored slightly better. The third test, however, was a test of 'word recognition.' In this test the score of the phonic group put them 4.6 months ahead of their 'normal reading,' which means, according to Mr. Tate, that they had scored 270 *percent better* than the word-method group. In other words, fifteen minutes of phonics for eight weeks had pushed them half a school year ahead of children taught by the usual method. Mr. Tate comments that this result is 'overwhelming proof of a reliable finding' and adds: 'Phonetic instruction and drill, as judged by the results of the Gates Primary Reading Test, Type 1, is far superior to the look-and-say method in developing the ability to recognize words.'"

Perhaps Flesch believes that silent reading and paragraph reading are tests of word "guessing" rather than reading. However, these aspects of reading are important both for children and for adults. Here are Tate's conclusions in full:

"1. Phonics instruction and drill as judged by the results of the Gates Primary Reading Test, Type 1, is far superior to the look-and-say method in developing the ability to recognize words.

"2. The results of Type 2 of the Gates test give a slight indication that the *look-and-say method is superior to phonics* instruction and drill in developing the ability to comprehend sentences.*

"3. Results obtained from Type 3 of the test show conclusively that the

*Italics mine (J. S. H.).

look-and-say method is superior to phonics instruction and drill in developing the ability to comprehend paragraphs of directions.*

"4. The use of as many as thirty minutes daily for special phonics instruction and drill leads to an unbalanced development of the abilities to comprehend words, to understand sentences, and to grasp the meaning of paragraphs.

"Other deductions that do not rest directly on the data and therefore do not have the weight of conclusions are, in the opinion of the investigator, justified. These inferences are: (1) Regular periods for phonics instruction and drill are not desirable. (2) Phonics should be used by the pupil as a tool and not as subject matter to be mastered for its own value. (3) Overemphasis on phonics hinders rapidity and thoroughness of comprehension."

Thus, out of four conclusions and three inferences, *only one favors phonics*. This is hardly what Flesch led us to expect!

We move on to experiment nine, a doctoral dissertation by Sister M. Dorothy Browne.[11] Flesch's discussion of the Browne experiment goes like this:

"Ten minutes-a-day of phonics for nine months has put them eight months of 'reading age' ahead of their fellow students. On the basis of her findings, Sister M. Dorothy Browne came to this conclusion: 'The study of phonics is helpful not only to the pupil who is deficient in reading, but is even more effective in stimulating the better reader to further growth.' "

Since Sister Browne's study is extensive, it is not feasible to quote all her results. One or two points should be made, however. First, she reports that *none* of her separate statistics were significant. Second, she points out:

"Granted that some phonic instruction is an aid to reading progress, it is desirable to note at what level of ability pupils profit most from such training . . . with the exception of the group with I.Q.'s 110 and above, the actual amount of gain made by the experimental groups varies little when classified according to I.Q. It would seem, therefore, that subjects with low I.Q.'s profit more by phonic instruction than those with higher."

Sister Browne found that a bright child profits more than a dull one, no matter what technique is used. Since dull children taught by phonics improved as much as the brighter ones (excluding very superior children) also taught with phonics, she recommends phonics for children with low I.Q.'s. The word method remains superior for normals.

Thus, three separate studies indicate that phonics is a good technique for training mentally retarded children. When evidence such as this begins to pile up in one direction, then the educator, the teacher, and the parent should take notice and act accordingly.

The tenth study is that of Dr. Donald C. Agnew.[12] Here again Flesch misleads his readers. Flesch quotes Agnew as follows:

"If the basic purpose in the teaching of primary reading is the establishment of skills measured in this study (namely: independence in word recognition, ability to work out the sounds of new words, efficiency in word pronunciation, accuracy in oral reading, certain abilities in silent reading, and the ability to recognize a large vocabulary of written words), the investigations would support a policy of large amounts of phonetic training. If, on the other hand, the purposes of teaching primary reading are concerned with 'joy in reading,' 'social experience,' 'the pursuit of in-

*Italics mine (J. S. H.).

terests', etc., the investigations reported offer no data as to the usefulness of phonetic training."

At this point Flesch stops quoting and says:

"I can fully understand Mr. Agnew's outburst of sarcasm, since I worked my way through the same literature. It's exactly as he says: If you want to teach children how to read, you need phonics; if you just want to make them feel good, you don't."

If Flesch had quoted the rest of Agnew's remarks, there would have been no question of sarcasm. Starting from the last of Agnew's quotation on this page, here is what Flesch omitted:

"It is possible that the aims of primary reading should embrace all these purposes. If this is true, the relation of phonetic training (and the abilities resulting from phonetic training) to these other purposes would have to be determined before the place of phonetic training in primary reading instruction can be ascertained."

Now, Agnew is saying that phonics *has* a place in reading instruction, but this place has to be determined in the light of *all* of the aims of our education system, not on the basis of mere mechanical skills alone. Until other investigators find new evidence to give to educators, the task of teaching reading should be met with the combination of techniques that seems most judicious in the light of present knowledge.

The eleventh and last study presented by Flesch is that of David Russell.[13] Flesch says:

"At the end of the experiment both groups were given twelve different tests of reading and spelling. The phonics-trained group did better on every one of those twelve tests. 'The table (of test results) clearly reveals,' comments Dr. Russell, 'that the early and rather direct type of instruction in the phonics group has a favorable influence on achievement in spelling and reading.'"

Again Flesch has failed to reflect the author's true opinion in the matter. Here is what Dr. Russell says:

"The results do not establish, however, a clear pattern of cause and effect relationships between phonetic instruction and successful visual and auditory perception. It is important to note that the teachers of the 'phonics group' used more than a phonetic method with an exclusive reliance on the sounds of words. Accordingly, it is not possible to say definitely that work in phonics improves visual and auditory perception as measured by the tests used or that practice in visual and auditory techniques necessarily is the cause of good phonetic analysis and high early spelling achievement. It would seem rather that the visual and auditory techniques are part-and-parcel of the program of phonetic instruction conducted in the classes studied, and that separation into cause and effect is unwarranted. The chief point probably is that primary pupils may acquire a group of basic word skills which are necessary for success in reading, spelling and other language activities. If these are not acquired in the early school years, there is evidence to suggest that a succession of failures and maladjustments seems almost sure to result. The present study emphasizes the importance, for spelling achievement, of acquiring a number of these language abilities early in the primary grades."

Russell points out that not only did the teachers of the phonics groups introduce phonics early, they also introduced handwriting early. This means that the results are contaminated because it is impossible to tell

whether the phonics group was better because of the phonics or because of the actual practice they had in spelling through their handwriting training. Unless this study is repeated with both groups having the same amount of training in writing, the results as Russell himself states cannot be attributed to phonics instruction alone.

DISCUSSION

All of the experiments that Flesch reports have now been examined. It should be clear that he has taken sentences out of context, misrepresented research, and built his case on insufficient evidence. The most generous judgment one can make of Flesch, after examining the ways in which he has contrived to argue the case for phonics, is that he ought to have known better. It does no service to either phonics or education as a whole to stoop to the tactics of the propagandist. The enthusiastic espousal of a theory is no excuse for journalistic irresponsibility.

Flesch has misled his readers by skillfully employing an arsenal of deceptions long familiar to trial lawyers, propagandists, and politicians. He has clothed his own ideas in the mantle of respectability with such misleading phrases as "(Phonics) . . . is the only *natural* system of learning how to read," implying that other techniques are *artificial;* or by such irrelevancies as: "I am not one of those people who call them (educators) un-American or left-wingers or Communist fellow travelers," implying that there are those who do. He does not bother to justify the terms he uses or dispel the aura of "obvious correctness" they create. He quotes passages from other writings out of context, conveniently omitting sentences which clearly contradict the interpretation he has placed on the quoted sections.

He has misstated problems, directing attention to limited aspects of an issue while ignoring the major part, and then professing to have settled the entire complex issue. He has "illustrated" his points with data which, on careful examination, turn out to be entirely inapplicable to the question at hand.

He has stated issues in ways which imply that there can be no middle ground between opposing viewpoints, thus forcing his readers to make a choice between trumped-up extremes —"pure" phonics or no phonics. Last, and most unforgiveable of all, he has not hesitated to cite falsehoods when they suited his purpose.

Flesch's book is engagingly written and has enjoyed heavy sales. A fairer, more objective book might not have been so amenable to attractive writing, nor rung up so spectacular a sales success. But it would have rendered a service to its readers, as does all good scientific writing.

What has Flesch really accomplished? (1) He has produced a great deal of unnecessary anxiety among many parents. (2) He has made the already difficult job of teaching even more difficult by forcing many schoolteachers to take time to reassure parents. (3) He has succeeded in writing a best-seller.

What is the reading situation in schools today? Arthur I. Gates, a leading educator, reports on the number of children reading today as compared with 1921. A study by Worchester and Kline showed that children in fifth grade in 1947 scored higher on a reading test than did

fifth, sixth, seventh, or even eighth grade children in 1921 when the phonics technique for teaching reading was at its peak.

In 1921, 237 children in every 1,000 scored so low that they were considered "poor readers," while on the same test in 1947 only 41 per 1,000 scored this low. This is an improvement of nearly 580 per cent. In 1921 only 6 in 1,000 scored high enough to be considered "superior readers" in comparison with 106 in 1947. Thus, using the same standards, eighteen times as many superior readers could be found in American schools after the word method had been inaugurated.

After writing a book which completely misrepresents not only the research done but also the actual educational level of schools today, Flesch caps his argument in this way:

"There are one or two dozen textbook houses in America. By far the most lucrative part of their business is the publication of readers for elementary schools. There are millions of dollars of profit in these little books. Naturally the competition is tremendous. So is the investment; so is the sales effort; so is the effort that goes into writing, editing and illustrating these books. . . .

"Naturally, the stupendous and frighteningly idiotic work of concocting this stuff can only be done by tireless teamwork of many educational drudges. But if the textbook house put only the drudges on the title page, that wouldn't look impressive enough to beat the competition. So there has to be a 'senior author'—someone with a national reputation who teaches how to teach reading at one of the major universities.

"And that's why each and every one of the so-called authorities in this field is tied up with a series of readers based on the Chinese word-learning method. As long as you used that method, you have to buy some $30 worth per child of Dr. So-and-So's readers."

So Flesch would have us believe that the reason why Johnny can't read is a sort of conspiracy between unimaginative educators and money-mad publishers. It would take a credulous person indeed to believe that. And surely these are strong words for a man who must have realized thousands of dollars from a book which, in our opinion, has done more to mislead the public than any other book in recent educational history.

I am indebted to Saul W. Gellerman for his assistance in the preparation of this paper.

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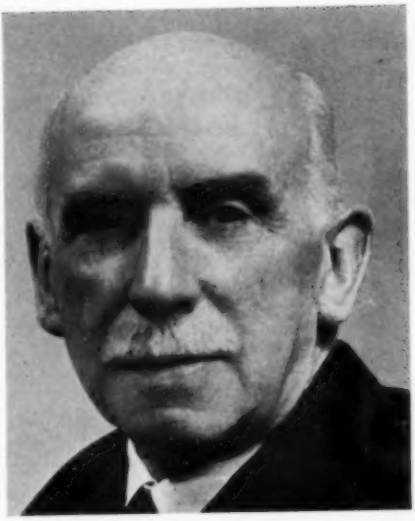
Pediatric Profiles

Sir Leonard Gregory Parsons

(1879-1950)



LEONARD GREGORY PARSONS was, as they say in England, born and bred a Midlander. He started life not far from Shakespeare's Stratford-on-Avon; and between this time (1879) and his death in December, 1950, he must have gone over every yard of the Midland Counties of Worcestershire and Warwickshire, and particularly the large city of Birmingham.

His life was essentially governed by Matthew 16:26: "For what is a man profited, if he shall gain the whole world, and lose his own soul?" Over and above all his vast and multifarious professional interests, he was an ardent nonconformist churchman, coloring his thought and action by the words of the divine physician, St. Luke. These matters were always clearly evident and it was no easy thing to penetrate the mind and personality of "L.G." unless you were rather well informed on the real background of the man.

His early education took place in a famous school, King Edward's Grammar, the foundation of which went back nearly 300 years. In this nurture, coupled with a good home background, he had a happy boyhood and early adolescence and "L.G." gradually absorbed the sense, wisdom, and character-making which was to mature in a yet almost wholly unanticipated manner. He learned that life's successes and contentments depend so much upon a healthy mixture of hard work and good play. He early acquired some reputation in the athletic world and could cover a hundred yards in commendable time. His rather thin but agile figure cut down skin resistance to a minimum and an adaptable art of muscular and postural relaxation, with immediate ability to tone up to an athletic status,

Photograph courtesy the Photographic Department of the Birmingham Children's Hospital.

never really deserted him, so that while he rarely moved in a precipitous manner he coordinated his body tempo in some strict correlation with his mental tempo; alertness combined with an ever-present sense of tonic well-being.

As a young man he was a keen cyclist and covered most of the British Isles. His rugby football was first class, but he could never convince his mother that it was not a heathen game. He was the fastest 100 yard sprinter in Great Britain in his day and defeated an American champion about the year 1900. "L.G." played tennis till he was 70. He steadfastly refused to indulge in swimming; he always said that he would go into the water when he could swim, but not until!

He early resolved to strive and see and know something of the wonders of the world rather than to be found "living sluggardized" and wearing out his youth in "shapeless idleness." "L.G." 's life was not overplanned, but he early accepted opportunity with its attendant responsibility. Thus he entered Birmingham University and graduated M.B., B.S. London in 1903, and M.D. in 1908.

During a relatively short period of hospital internship, at least two significant things happened. The first was his continued love of cricket. Of course, in those days the interns received no payment but each had to be "professionally dressed." Thus, one day "L.G." arrived at Lord's cricket ground to see a test match with Australia; he had been given a ticket to the grandstand which required frock coat and top hat—which he borrowed. When he arrived at the ground, he was told that the ticket admitted him to the grandstand but not to the ground. The cost of admission was 1/– which he did not have. On this occasion he did what he usually did—pawned his watch and saw the game in comfort!

Second, "L.G." realized that if he was really to get at the backbone of practical affairs he must get into the homes of the people and see more of common life and the realities of human relationships. Thus prompted, he moved into general practice and soon started to find out more and more about the ups and downs in the day-to-day life of the busy family doctor in residential and in industrial areas. He soon recognized that disease in infancy and childhood was not only rampant but hardly understood. His sensitive nature became very sensitized to a great need. This even, at times, created within him some anxiety as on the numerous occasions upon which he sought special assistance in domiciliary obstetrics at the slightest pretext, fearing, quite rightly, that even the most minimal but preventable risks of birth injury should be prevented. With these attitudes being engendered, little did "L.G." realize that eventually and in his full maturity, he would be elected a Fellow of the Royal College of Obstetricians and Gynaecologists, *honoris causa*.

"L.G." now began to see his real clinical strength. He moved into hospital again—The Hospital for Sick Children, Great Ormond Street—and roamed the place first on the wards as resident medical officer and followed this by exercising his mind in that great testing ground of abilities, the large casualty department. He made it. He saw new ways of saving life. He now knew that urgent, early,

and accurate diagnosis was the real key to successful treatment. The surgical aspects of acute disease thus impressed him very much, and for this and other reasons he always found pleasure and satisfaction in consultation with his surgical colleagues and was greatly respected by them for his shrewd opinion and guidance.

In those days (1910) the term "paediatrics" was not much used in England, and practice in "diseases of children" was, of course, engulfed in the general practice of the family doctor, or was included in the sphere of action of the general physicians and general surgeons. "L.G." had acquired the M.R.C.P.(Lond.) and thus was almost stamped, if he so chose, to become a consulting physician on a hospital staff. Finance was difficult and the honorary posts were quite unpaid. While recognizing *ars longa, vita brevis,* he stuck it out and made up his mind that he would pioneer. He got on as physician to outpatients to Birmingham Children's Hospital (1910) and the General Hospital for Adults at about the same time.

He was now well in the swim; he could re-educate himself in the advances in physiology, in the changing scene in many things—bacteriology, the help from the new radiology, the improving ideas and facts in nutrition and the earliest dawn of biochemical matters and thoughts which Cannon later epitomized in the famous term "homeostasis." Clinical material, in the rapidly expanding industrial city of Birmingham, was almost unlimited, in fact bewildering to the man "L.G." who was trying more and more to see some order in the chaos of the severe and numerous pathologies coming before his eyes each day. He knew he was the man to get things going, and he did. He got the students around him in the Children's Hospital (a new idea then) and did so many good things by precept and by example that his hospital colleagues recommended to the University of Birmingham that "L.G." be given a special status; thus he was appointed the first "Lecturer in Diseases of Children" in 1915, and while he continued for many years as a teaching and practicing general physician (and his knowledge of adult medicine was rarely lacking) his heart and soul were in his beloved Children's Hospital into which he poured enormous energy and drive, not least with the forces of honest and persuasive ability in the lay committees.

He now had a young man's vision—"young men shall see visions, and your old men shall dream dreams" (The Acts, 2:17.)—he often quoted this in his later years. He was pure at heart. This was all quietly and ably encouraged by his noble wife (later Lady Ethel Parsons) who could well see that "L.G." had immense power for good in many things. This ability was, strangely enough, first recognized by the Royal College of Surgeons and he was invited to give the Arris and Gale Lecture, which he did on "The Mechanism and Treatment of Shock"; a subject which had struck him as highly significant in the final cause of death in so many infants and children afflicted with injury, violence, or overwhelming infection. Two years later, when the First World War started, these ideas on shock assumed great importance and were followed by extended researches by many others in the physiological aspects of shock.

From 1914 to 1918 "L.G." was with the overseas R.A.M.C. and spent much time on the Serbian front, much more involved with tackling malarias and blackwater fever and other epidemiologies of the army in the field than with wounds. Under the very difficult conditions of this campaign he remained the typical student and explored the factors concerned in the renal and cerebral complications and other malignant aspects of *Plasmodium falciparum*. He was awarded the Serbian Order of St. Sava. This four-year disruption from his main stream of thought gave time for reflection. He had already made known his interest in growth and development by a paper on "Infantilism Associated With Chronic Interstitial Nephritis" in 1911. Nutrition in its clinical and biochemical aspects was to command his exploring mind much more.

However, on return to England in 1918, energized even more, he plunged into improving his Birmingham Medical School, and especially the teaching of "diseases of children" (a very limiting term but usual then, and even now—1955—in some backward places, retained!). He started regular and organized teaching rounds, and tutorials and undergraduates saw at once its high importance and encouraged "L.G." by their keen and appreciative attendance. They saw that here was a man who knew the ropes and had got his teeth deep into the matter from the clinical and the academic aspects.

This was the start which led up to the evolution of a Department of Paediatrics second to none in the British Isles, finalizing as a mecca for professional visitations from many European countries and the United States and Canada and Australia. Continued happiness was "L.G." 's keynote. In his presence one felt a sense of security. His constant aim among all with whom he worked was to understand and be in mental and intellectual affinity. Yet it was easy to upset his sensitive and, in some ways, shy and retiring personality. A joke had its place, but only its right place. Denigratory or insincere remarks might call forth an emotional pallor and quickening of the facial expression with a slight shrug of the shoulders which spoke more by way of derision than any vocal effort.

"L.G." had that great asset of the successful "children's doctor," the right voice, in tone, tempo, and tolerance, the sure initial way to the child's heart, and understanding. Those of us who saw and heard all this were being gradually educated into the overt, and yet sometimes mysterious, total humanity of the man. The science and the art of medicine was seen in a tenacious equilibrium and it was self-evident that a new brand of teacher was with us—one who pictured life in its broadest setting and at the same time saw a humanitarian philosophy permeating his daily round of what to others may have been more like a common toil. "L.G." was an excellent "diagnosis" doctor, and this was interesting since, as I have already said, he ranged over the whole Seven Ages of Man. It was a little strange perhaps for him to say, "I saw a man aged 65 yesterday evening —remarkably good case of Weil's disease," or "I am very suspicious that Mr. X. has an early carcinoma of the lung although there is no radiological evidence." Sound judgment indeed.

But he was constantly exploding the idea that a baby was only a miniature adult, and he agreed (with Wordsworth) that environmentally and by way of all nature the child was often "father of the man." One felt that he hung on to his whole range of clinical practice and teaching, so that he could the more expound upon the nature and longitudinal history of disorder or disease as it may be started in early life and move on, unless recognized early and properly controlled, to a relentless upset of physical or mental health in later years.

This was a wise plan and gave greater strength to his students' comprehensions and incidentally showed that the proper study of mankind is not only his diseases but his biology, his ecology, his place in nature, and how continued health is a great positive achievement. Thus, he sowed many seeds of erudition in these teaching years and the Clinical School was so uplifted that pediatrics ultimately became a major part of the qualifying examinations. Around this reputation, and concurrently, voluntary subscriptions flowed in for a new biochemical research department and later a cubicle isolation unit of sixty cots was put up to give added scope to the newer studies of disease in infancy. This building, "Leonard Parsons Block," and so labeled in clear big lettering, is now a lively affair and carries on the great tradition in permanent memory.

The early struggles to understand where we were clinically in 1924 are revealed in "L.G." 's now rather famous Goulstonian Lectures in "Some Wasting Disorders of Early Infancy." This was a brave attempt to set down rational views out of the relative chaos of the time, and although humbly confessing that his arguments might fail to carry conviction because "I have not builded well," he moved on to say that "however the initial loss of weight has been produced the continuance of the atrophic state depends upon an altered metabolism and not upon disorder of digestion and absorption." Here is suggested light on our present-day knowledge of renal, hepatic, and other visceral enzyme and electrolyte factors in some "marasmic" states. In this biochemical research he was ably encouraged and assisted by Dr. Evelyn Hickmans.

Radiology intrigued "L.G." The structure of bone in health and disease caught his attention. It was a delight to hear him expound on the translation of the osteoid tissue into the normal pattern and this happily synchronized with the recognized effects of ultraviolet light on the dermal sterols and the full fruition of Edward Mellanby's experiments on rickets in dogs and the ultimate isolation and synthesis of calciferol. Having known Sir Thomas Barlow, "L.G." had more than a passing interest in scurvy, and circumstance had it that while Sir Norman Haworth, professor of chemistry in the University of Birmingham, first synthesized ascorbic acid in 1933, "L.G." was able to demonstrate to the Royal Society of Medicine in London in the same year the first case of scurvy cured by prescription of this ascorbic acid. In his papers "Coeliac Rickets" (1927) and "Rickets and Allied Diseases" (1928), biochemical ideas emerged touching on malabsorption deficiency in the one compared with the "entirely endogenous origin of the other—renal rickets."

"L.G." was a good listener. He listened to a colleague (Dr. Auden) relate a story about recurrence of icterus gravis in some families. It was not long before "L.G." postulated that icterus gravis, hydrops fetalis, and hemolytic anemia of the newborn were manifestations of a hemolytic process (1933). This built into Landsteiner, and Levine's later discoveries led to confirmation of this. "L.G." objected to some initial suggestions that it should be called Rhesus disease (his letters in the *Lancet* vehemently rejected the term) and his own suggestion of hemolytic disease of the newborn was finally accepted. He was always worried as to whether the brain cells in kernicterus were stained because they were dead or died because they were stained. He and his colleagues got into long and cyclical argument over this, the end of which only came when that learned pediatric pathologist (Dr. Heinrich Barr) stepped in and said it was due to a hepatoencephaloclastic process! We thus succumbed and even today we are more or less in status quo on this. However, his troubles about kernicterus, even after transfusion with Rhesus negative blood, were happily overcome, as he lived to see the grand success of Diamond's exchange replacement technique.

Notwithstanding all the eminence he achieved, "L.G." always seemed to know about the latest local news and social events about twenty-four hours before most people: he had an uncanny habit of absorbing to his mind any local "scandal" and it was more than likely that a "secret" had got round to him before anybody else. And it was dangerous to assume that he was uninformed even on the latest social visit of a ward sister with an enterprising intern! To be the first communicant to him of a bit of subtle news was a revelation—his whole body would take it up with a sense of real satisfaction (or possibly dissatisfaction), and the inner, lovable, humble and yet shyly reticent man would cast a smile which would include just that amount of orofacial movement to raise his ever-trim moustache the appropriate amount to give a final gesture or another added touch to his vast store of wit, and which gave "L.G." that other wave length to indicate and remind us at other times that he was a most human of human beings. He was heard, when emotionally stressed on one occasion, to say "damn"—but quickly and effacingly said he meant to say "damsons"!

Like most men, he had a subconscious hero-worship. He modeled much of his understanding of life on his revered and senior colleague, Dr. James Russell, but he looked for some light relief to the endless and side-splitting tales and stories of his friend, Dr. Kenneth Wilkinson, also of the Birmingham Children's Hospital. Two things "L.G." did: he always drove his own car (except in much later years he actually was occasionally seen being driven by his distinguished son, Dr. Clifford Parsons), and he never touched alcohol. It is reported that he once smoked a half cigarette, but the resultant vaso-vagal reaction set him against it for the rest of his life. He had little sense of mechanical things or of the more modern gadgets of medical enquiry, but he gave due credit to those who handled them. His fragile and often fragmented stethoscope would have alarmed even Rene Hyacynthe Laennec himself, but

"L.G." was a master of the auscultatory art, and an uncanny habit of suspecting and detecting the rather occult interlobar empyema. He became virtually one of the leaders of his profession in England. Thus, he was wisely chosen in 1945 as Dean of the Medical Faculty and became duly installed in the beautiful walnut-paneled room of the then new Medical School at Edgbaston.

Many visitors from the United States arrived in Birmingham to look up "L.G."—I remember Kenneth Blackfan, G. Mitchell, and others, being caught up in an unexpected whirl of movement doing their best to keep up with "L.G." 's tour of the hospital. His real friendship with these and others like Ned Park, Alan Brown, and Rustin McIntosh warmed his heart, and he was proud of his connection with the American and the Canadian pediatric associations, especially as he himself was a founder member of the British Paediatric Association (in 1928) and its President during the war years, 1942-1945.

Visits to Lakeland in Cumberland were "L.G." 's main holiday paths, and he knew all the ins and outs of these rather complex mountains, and his roaming and climbing were reminders of his sustained power: and even in such isolated places he would set going a snappy chat as to why the chlorides fell in the blood and cerebrospinal fluid in acute pneumococcal pneumonia, or, to change the subject, start us off on the good and the bad of the ethics of the profession. And how happy we all were, knowing that after a few hours of muscular and cerebral wear and tear, we should land back to a magnificent "jam and cream" tea at one of the remote farmhouses which "L.G." knew all about. Then there were the visits to the memorial theater at Stratford-on-Avon, a few of us gathered together to extend an appreciation of the inexhaustible fame of our beloved Shakespeare.

So time marched on in the interwar years. The rather exclusive morning coffee with the Children's Hospital Matron (Miss Cockeram) and the Secretary (Mr. Shrimpton) became a ritual at which big hospital business was considered, and most of the committee questions were worked over, so that the clear and concise schemes and answers were nimbly presented. This was a powerful and impressive trio. Nurses' homes were rebuilt, research departments were extended. Experimental rat rooms were made, as this was the period when "L.G." went in for extended studies in dyshemopoiesis. He regarded it as a period extending upon the renaissance of hematology created by Minot and Murphy. A series of papers, parts I to X, appeared in the *Archives of Disease in Childhood;* "regenerative factors in bone marrow" were considered; new words such as "anhemopoietic anemia" or "erythronoclastic anemia" were introduced; the former chaos of the anemias was being clarified into causes and effects and hence a lock-and-key precision in treatments proposed. Studies on reticuloses and some forms of generalized hemangiomatosis were made. Running concurrently was the preparation and publication (jointly with his surgical friend, Seymour Barling) in 1933 of the two volumes *Diseases of Infancy and Childhood.*

"L.G." was keenly interested in celiac disease and it was always a sure ground for hot discussion with visiting

American colleagues, whether it was primarily a fat intolerance (as we English believed) or whether it was a carbohydrate intolerance (as opinion went with the Americans). He instituted an enormous amount of biochemical analysis and balance experiments to trace the elusive factors of the steatorrhea, and he pursued the clinical problems in his Ratchford Memorial Lecture at the University of Cincinnati in 1931.

His wards were always a veritable clinical museum and were a constant reminder that the pediatrician, as Alan Moncrieff has repeatedly said, is ipso facto a general physician possessing the maximum degree of generality in outlook and practice. "L.G." continued to teach students in the adult hospital which was two miles across the city from the Children's Hospital; but between the two was the library of the Midland Medical Society, his settling ground for an egg-on-toast and cup-of-tea lunch in a quiet corner, while he ran through the journals and kept himself in close acquaintance with the latest, only to have to leave these absorbing occasions to move quickly on to his consulting rooms near by for three or four hours of fee-taking exercises (all his other work was entirely voluntary) and more often than not a round of domiciliary consultations up to fifty miles away, then back to a late committee or a hospital clinical meeting, and so to bed. The historical background of pediatrics gave added balance in his judgment of values. His knowledge scanned the time between Thomas Phaire (d. 1560) to G. F. Still (d. 1940), but "L.G." gave particular praise to Dr. Robert Whytt (d. 1766) for his "account of the symptoms in the dropsy of the brain" which was the first clinical description of tuberculous meningitis.

Like most men able to do all this, he had, as he himself said, a sure anchor at his home; no home was more enriched by husband and father; the comforts and graceful happiness within his family neutralized much of his fatigue, and his own spirit was uplifted daily by his inner soul and daily reading of the Bible. It was said that his Methodist religion ran like a theme of music throughout his speech, grave or gay, and indeed was woven into the full wholesome composition of his daily life.

World War II came. "L.G." was thrown into a near revolution of action. He was quickly caught up in the wholesale organization for handling military and civilian casualties. He became a key-man and was adviser in the heavily populated Midland zone. This heavy task took his mind away from clinical study for long periods, but he would drop into the Children's Hospital (which fortunately missed any bomb damage) and seek again some solace and satisfaction in a quick ward round with those of us who were left in charge; and it also lit up our sad hearts at a time when much of the City of Birmingham was lying in bombed ruins and death was all round about. At this time especially, "L.G." seemed endowed with perpetual youth, but, in truth, he had little time for relaxation.

"L.G." 's clinical interests were chiefly in matters of nutrition and moved gradually from older children to infants, the newborn infant and then to prematurity, and finally to antenatal pediatrics. He received the Moxan Medal (1942) of the Royal

College of Physicians for "the person who is deemed to have distinguished himself by observation and research in clinical medicine." The Blackader Lecture of 1946 on the "Effect of Ante-natal Conditions on the Newborn Child" focused new attention on the questions about the "bad egg in a good environment and the good egg in a bad environment" and brought up Shakespeare again (*The Midsummer Night's Dream*) in the "foul fiend Flibbertigibbet" (possibly German measles) who "gives the web and pin [cataract or corneal scar], squints the eyes and makes the hare-lip." And in his final series of Harben Lectures (1950) he moved in grand oration from "Historical Background: The Unborn Child" to "The Newborn Child and the Infant" to "The Older Child: A Glance Into the Future," humbly finalizing with Cecil Rhodes's last words—"So little done, so much to do." He was reminded of Milton's lines on the death of a fair infant of a cough—"O fairest flower no sooner blown than blasted; Bleak winter's force made thy blossome dry."

As his friend, Lionel Hardy, noted, honors came to "L.G." steadily, inevitably, and in full measure—a Knighthood, the dedication in his honor of a wing of the Children's Hospital, and finally, perhaps the greatest of all, the Fellowship of the Royal Society. Only a few weeks before his sudden death, he delivered, on St. Luke's Day, the Annual Oration given in memory of William Harvey (1578-1658); he spoke on "The Influence of Harvey and His Contemporaries on Paediatrics," sketching in masterly fashion the glorious seventeenth century which contained not only Harvey, but Francis Glisson, Sir Thomas Browne, John Mayow, and Thomas Sydenham, and others who were even then making their contributions to the study of children in health and disease. "L.G." had followed in his work Harvey's injunction—to seek out the secrets of nature by way of experiment.

His successor to the Chair of Paediatrics in Birmingham, James Smellie, has recorded that "L.G." maintained a flexibility of intelligence, vigor, and energy, which were intrinsic features of his genius all his days. After the sudden departure from our midst on Sunday morning, December 7, 1950, just after his customary attendance at church and among his family in his home, we were reminded that "holiness not merely energizes; by its reinforcement of the will it wrings from the body the uttermost drop of service, and secures a vital vigor to the last."

A. V. Neale

Comments on Current Literature

NOCARDIOSIS

THE possibility of making an unusual diagnosis in medical practice is always a challenge for the practitioner of medicine, and if this diagnosis carries with it the possibility of successful therapy, the experience is gratifying indeed. Such seems to be the case in the recognition of infections with the nocardia, fungi which affect not only animals, but man as well. *Bergey's Manual of Determinative Bacteriology*[1] lists thirty-three species of nocardia, and emphasizes the generally accepted distinctions between the nocardia and the group of the actinomyces.[1, 2]

A stimulating article on nocardial infections by Weed, Andersen, Good, and Baggenstoss[3] appeared recently in the *New England Journal of Medicine* (Dec. 29, 1955). These authors report their experience with seven cases of pulmonary nocardiosis, two of these patients being in the pediatric age range, a 7-year-old boy, and an infant of fifteen months. They point out that nocardiosis may resemble closely "other suppurative conditions due to such varied agents as klebsiella, pasteurella, salmonella, malleomyces and actinomyces."[3] In their patients pulmonary disease was the initial problem. When sputum was present, it was usually thick and sticky, and either purulent or mucopurulent. These findings suggested the respiratory tract as the most likely portal of entry for the organism. However, as the authors state, a review of the literature reveals that the organism has been cultured from almost every part of the body, and that the nocardia may gain entrance not only by the respiratory route, but through the gastrointestinal mucosa and even through breaks in the skin. The central nervous system is a frequent extrapulmonary site of the disease, with consequent grave prognosis. In two of the seven cases described, there was central nervous system involvement with intracerebral abscess formation.

Roentgenologically there is nothing distinctive about the pulmonary involvement which would be pathognomonic on roentgenographic grounds alone. The only diagnostic laboratory procedure is bacteriologic demonstration of the organism, and it is upon this that the authors place emphasis. In their opinion nocardiosis should be suspected when a pneumonic process does not respond to the usual antibiotics. As the disease process continues, the roentgenographic appearance resembles most closely that of tuberculosis. If the clinician is alert to the possibility that his patient may be suffering from nocardial infection, it is his responsibility to secure adequate material for culture. The authors stress the fact that the microbiologic aspects of the nocardia are well known, and that with proper material obtained for culture, the laboratory diagnosis of this disease is not difficult. It is of some importance that these organisms have a wide distribution in food substances, and may be present in gastric washings without etiological significance. If, however, the organism is cultured with ease from gastric washings on repeated occasions, or obtained from sputum, particularly from material aspirated from the tracheobronchial tree, the diagnosis of nocardiosis can be established readily.

The authors believe that under certain circumstances it may be advisable to undertake a lung biopsy in order to ensure adequate culture for tubercle

bacilli, various fungi, and for unusual bacteria. The possibility of amebic infection should be considered, as well as chemical causes of pulmonary disease, such as beryllium, silicon, and barium. Obviously lung biopsy is not indicated routinely; however, in the carefully selected case, such a procedure might be highly desirable, and indeed might provide the evidence on which lifesaving therapy is instituted.

It is interesting to note, in a brief section on the pathologic aspects of nocardiosis, that the main histologic change was necrosis of tissue with the formation of confluent abscesses and the absence of encapsulation. The lesions studied did not resemble those of the granulomas. Although necrosis was prominent in the disease process, it was not associated with the formation of epithelioid cells, nor was it accompanied by the formation of granulation tissue. Giant cells were infrequent, being observed only occasionally. Such pathologic features of the disease would certainly account for the tendency to spread, and emphasize again the need for early and accurate diagnosis in the nocardial infections.

A most heartening aspect of this important paper concerns therapy; these patients respond well to sulfadiazine, whereas the disease process does not seem to be affected by the usual antibiotics, such as penicillin and the tetracycline compounds. Extensive laboratory studies in mice were carried out in 1951 by Strauss, Klingman, and Pillsbury.[4] Of a large series of therapeutic agents tried, sodium sulfadiazine gave 100 per cent protection against death from infection with *Nocardia asteroides* when administered in a daily dosage of 50 to 100 mg. per kilogram of body weight. Three of the seven patients reported by Weed and his associates received sulfadiazine, one for three months and the other two for a period of five months; in each instance, the patient responded well. One patient, a 26-year-old physician, whose initial diagnosis had been that of tuberculosis, responded remarkably to sulfadiazine, once the diagnosis of nocardial disease was made; after five months this patient was able to return to work and has remained well since 1946. A second patient who received sulfadiazine recovered completely from nocardiosis, but died subsequently from another unrelated disease. In the case of the third patient treated with sulfadiazine, the pulmonary lesion cleared roentgenographically under the influence of the sulfa drug, but the patient died as a result of central nervous system involvement—cerebral abscess due to *Nocardia asteroides*.

The authors' summary is pertinent and well stated: "Intensive efforts should be made to determine the etiologic basis of any intrapulmonary infection that fails to resolve on antibiotic therapy. The diagnosis of nocardiosis can be made only by isolation and identification of the organism from suitable clinical material. Such material may need to be obtained by bronchoscopy or even by biopsy of pulmonary tissue."[3] While, in general, nocardiosis may be a rare disease, the importance of early diagnosis in order to avoid spread of the fungus to other parts of the body, particularly the central nervous system, and the ready availability of sulfadiazine as a simple and remarkably effective therapeutic agent, should encourage the practicing physician to keep this disease in mind as a possibility in conditions, especially pulmonary conditions, which are not responding under the usual therapeutic regimen.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

I am writing in regards to my article, "Pediatric Rehabilitation and the Pediatrician," which appeared in the October issue of THE JOURNAL OF PEDIATRICS.

It seems necessary to correct a misinterpretation which may arise. There is no thought that the pediatrician arrogates to himself the final decision in regards to operative procedures by either the orthopedist or the urologist. Needless to say, all specialists working on such a team are generally imbued with the group approach. All decisions are made by the group, with the greatest part of the responsibility for an individual procedure resting on the surgeon involved. The chief function of the coordinator is to make certain that the proposed operation is fully discussed by all other specialists concerned with the welfare of the child.

It may be well also to emphasize that the role of the coordinator on such a team requires long experience and study. It is also true that the whole problem of teamwork and coordination is still an open one and we have by no means attained a final opinion as to the best way in which such a team can be administered.

There is, in addition, a technical correction to make. The sentence on page 468 at the beginning of the lower third of the first column reading "The question arises as to a concomitant abductor neurectomy" should read as follows: "The question arises as to a concomitant post-tibial neurectomy (Stoeffel operation)."

ABRAM KANOF, M.D.

News and Notes

Dr. Royal Storrs Haynes of New York died January 19, 1956. He had retired several years ago and was 78 years of age. After graduating from Cornell he received his medical degree from Columbia (P & S) in 1903. For a number of years he was clinical professor of pediatrics at Columbia. One of his chief interests was the New York Academy of Medicine, serving as secretary from 1918 to 1924, and as a trustee from 1925 to 1929. During World War I he was director of the Junior Red Cross in France. He aided in the establishment of L'École de Puericulture in Paris, and was made a Chevalier of the Legion of Honor by the French government. He was supervising editor of a series of pediatric monographs by various authors published in 1926. For many years he had been interested in posture in children and the correction of postural defects. He was a member of the American Pediatric Society.

The **Sixth Congress of the International Society of Hematology** will be held in Boston during the week of August 26, 1956. A circular of information with a detailed announcement of the program may be obtained from Dr. James L. Tullis, New England Center Hospital, Harrison Avenue and Bennet Street, Boston 11, Massachusetts.

A Summer Camp for Diabetic Children will be opened for the eighth season under the auspices of the Chicago Diabetes Association, Inc., from July 15, to August 5, 1956, at Holiday Home, Lake Geneva, Wisconsin. Boys and girls aged 8 through 14 years are eligible. For further information regarding fees, interested persons should write The Chicago Diabetes Association, 5 South Wabash Avenue, Chicago 3, Illinois.

Two postgraduate courses in Pediatrics are being offered by the **Department of Pediatrics, Harvard Medical School,** at **Massachusetts General Hospital** in June, 1956. The first, which will be from June 11 through June 19, will deal with general pediatric problems exclusive of endocrine and metabolic disorders. The second, June 20 through June 22, will deal specifically with parenteral fluid therapy, management of nephritis and nephrosis, diabetes, disturbances of growth, and related endocrine disorders in children and adolescents. Enrollment may be for either course or the total combined course. Those interested should write: Courses for Graduates, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts.

The **Intermountain Pediatric Society** will hold its annual convention in Sun Valley, Idaho, June 7, 8, 9, 1956. Guest speakers will include Dr. Douglas N. Buchanan, Chicago, Ill.; Dr. Amos U. Christie, Nashville, Tenn.; Dr. Wm. L. Hewitt, Los Angeles, Calif.; Dr. Horace L. Hodes, New York, N. Y.; and Dr. Edith L. Potter, Chicago, Ill. The meeting is open to all physicians.

The **Department of Pediatrics of The Ohio State University** and **The Children's Hospital of Columbus, Ohio,** announce the establishment of a Clinic of Child Development which will concern itself with deviations from normal behavioral development in the preschool period from birth through 5 years. In addition to diagnostic evaluation, guidance in the management of problems and help in securing the necessary medical and community services will be provided. Fellowships for a period of one year, with a stipend of $5,000, are available beginning July 1, 1956, with one position each six months provided. Pediatricians who are trained will have opportunities to engage in research projects designed to elucidate the etiologies of the neuropsychiatric disabilities of childhood and to enter into the teaching program. Address inquiries to Dr. Earl H. Baxter, Chairman of the Department of Pediatrics, The Ohio State University, or to Dr. Hilda Knobloch, Associate Professor of Pediatrics and Director of the Clinic.

Books

Special Education for the Exceptional. Edited by Merle E. Frampton and Elena D. Gall, Boston, 1955, Porter Sargent Publisher. Three volumes, price $5.50 each.

By the term "exceptional" is meant the individual who deviates physically or mentally from the normal to such a degree that special education is necessary or desirable. To this encyclopedic discussion of special education nearly 70 authorities interested in some particular aspect have contributed.

Volume I is a general discussion, presenting chapters in the educational problems involved, the training of teachers, administrative matters, and the like. While it is not possible to obtain exact statistics of the number of exceptional children, it is estimated that special education is indicated in from 9 to 14 per cent of the children of school age in this country.

Volumes II and III are of more interest to the physician. Volume II considers the educational problems and methods for exceptional children with physical handicaps. Thus there are chapters on the blind and partially sighted, the deaf, the child with speech defects, the orthopedically handicapped, and the child with rheumatic heart diseases. Among the subjects included as special health problems are muscular dystrophy and tuberculosis. Volume III takes up emotional and mental deviates. Both the intellectually gifted, and the mentally retarded child are considered in sections of this volume. Other sections or chapters include the child with a brain injury and the epileptic. The discussion of the educational problems of the emotionally disturbed child contains a chapter on juvenile delinquency.

While the books are of more interest to the educator than to the physician, it is an important work of reference for the latter, who so frequently is asked for advice on the physical problem. Not the least important of his responsibilities is a knowledge of how the accompanying educational problem for the specific child is best handled. There is much overlapping in the field of special education and it is interesting to note the breadth of view of many of the contributors who themselves have a special interest in some one field.

Editor's Column

THE TUBERCULOSIS RENAISSANCE

ONE of the factors that make medicine such a fascinating vocation is the constantly changing picture in the incidence and relative importance of various diseases, and as a result the changing interest in a specific disease. There is always something new coming to the forefront which keeps the physician alert, and saves him from the boredom of routine. Congenital syphilis and congenital cardiac disease are examples of how the pediatrician's interest waxes and wanes. Some thirty to forty years ago pediatric textbooks devoted much space to congenital syphilis, and the current medical literature was replete with discussions of one phase or another of the disease. At that time the discussions of congenital cardiac disease were quite limited and chiefly of a descriptive pathological nature. With the advent of the arsenical drugs and later the antibiotics, the clinical importance of syphilis decreased rapidly, and it has become almost a rarity rather than an important clinical problem and is only occasionally the subject of a discussion in current medical literature. While the interest in syphilis was declining, advances in diagnostic methods and cardiac surgery have made congenital cardiac disease one of the topics most frequently discussed today. In the last edition of one of the standard pediatric texts almost ten times as much space was allotted to the discussion of congenital cardiac disease as to syphilis—a complete reversal from some earlier editions.

Tuberculosis is even more striking in this respect, as the cycle of interest shows a more variable curve. Some forty to fifty years ago tuberculosis was one of the most important medical problems that existed in the United States, and our hospital beds were filled with children with one form or another of tuberculous disease. Then came a steady decline in the morbidity and mortality and, coincidentally, general interest steadily waned. No great interest ever developed in this country over BCG vaccination, in contrast to what occurred in many countries where the epidemiological picture and tuberculosis problem were quite different. Pediatricians, as a group, took relatively little interest in the disease.

A few years ago pediatric interest was again aroused with the introduction of streptomycin for the treatment of tuberculous meningitis, a condition which previously had been looked upon as invariably fatal. This led to a marked increase in the number of discussions and reports in current medical literature, reflecting a revived interest in tuberculosis.

With the discovery of isoniazid in 1952, an entirely new interest has been stimulated, bringing with it new conceptions of tuberculosis control, as well as for the treatment of the various clinical forms of the disease. In this issue Dr. Hsu, of Baylor University, Department of Pediatrics, presents a discussion of these recent developments and the newer concepts of tuberculosis control, which is of particular interest

to the pediatrician. How recent is this interest and development is well shown by the references: over 50 per cent refer to studies published in the past two years, and 90 per cent published since 1951. Dr. Hsu makes a strong case for routine tuberculin testing in infancy and childhood, and the use of isoniazid in the treatment of the primary tuberculous infection in childhood. Her discussion gives an excellent background for an understanding of the many papers on the subject which are bound to appear in the next few years. An important field has been opened for investigation.

READING DIFFICULTIES

ONE of the most frequent causes of emotional disturbances and behavior disorders in school children is difficulty with reading. Although the concept of a definite clinical syndrome —specific reading disability—as the basis for most reading difficulty is relatively recent, the problem is an old one. It has troubled educators for many years and has been the subject of much study and experimentation.

The "reading problem" has been brought to the attention of the public by Rudolf Flesch's recent best seller, *Why Johnny Can't Read*, which was widely syndicated in the newspapers and in this way received remarkable publicity. Because of this publicity parents are turning in increasing numbers to their pediatricians for counsel.

Flesch is critical of American teaching methods and American reading ability. He accuses the United States public school system of abandoning the phonics, or letter-by-letter, syllable-by-syllable, method of teaching reading for the whole word, look-and-say, or memorizing words as wholes method. To the exclusive use of the whole-word method, introduced about 1930, Flesch attributes the poor reading ability of our school children.

Educators, almost unanimously, disagree sharply with Flesch. They hold that American children read as well as, if not better than, their parents and grandparents, despite the larger classes, the almost universal school attendance, compulsory school attendance of children of low mentality, automatic promotion, and so on.

The problem of the nonreader and the poor reader is an old one. It is said that John Hunter was unable to read until he was 17 years old. Dr. May Lazar, Assistant Director of Research in the New York Public Schools, has called attention to a report of the New York schools in 1904 which points out that only 30 per cent of the pupils who entered the 1A grade reached 8B. In a report in 1838 Horace Mann says, "More than eleven-twelfths of all the children in the reading classes in our schools do not understand the meaning of the words they read."

Elsewhere in this issue of the JOURNAL Hobkirk examines the evidence on which Flesch bases his thesis. She points to numerous misinterpretations, inaccuracies, and irrelevancies. Parents can be made unnecessarily anxious by half-baked information about their children's education just as they can about their health.

H. B.